

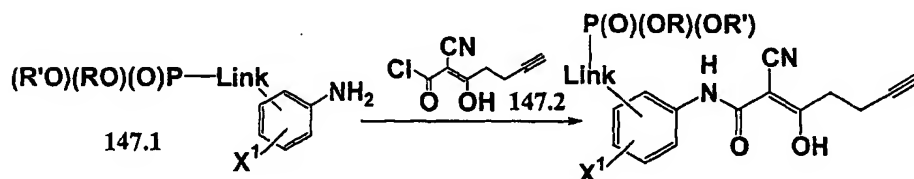
phosphonomethyl substituent, by reaction with a trialkyl phosphite at 120°, to prepare, after deprotection of the side chain and chlorination, the 21-chloro phosphonates **146.17b** and **146.18b**. The Arbuzov reaction is described in Handb. Organophosphorus Chem., 1992, 115-72. In the procedure, the substrate

5 is heated at from 60° to about 160° with a five to fifty-fold molar excess of the trialkyl phosphite. Using the above procedures, but employing, in place of the dibromide **146.14**, different dibromides, the products analogous to **146.17b** and **146.18b** are obtained.

10 **Example 147 Preparation of Representative Compounds of the Invention**

Representative compounds of the invention can be prepared as generally described by Westwood et al, *J. Med. Chem.*, 1996, 39, 4608-4621, and according to the following general route.

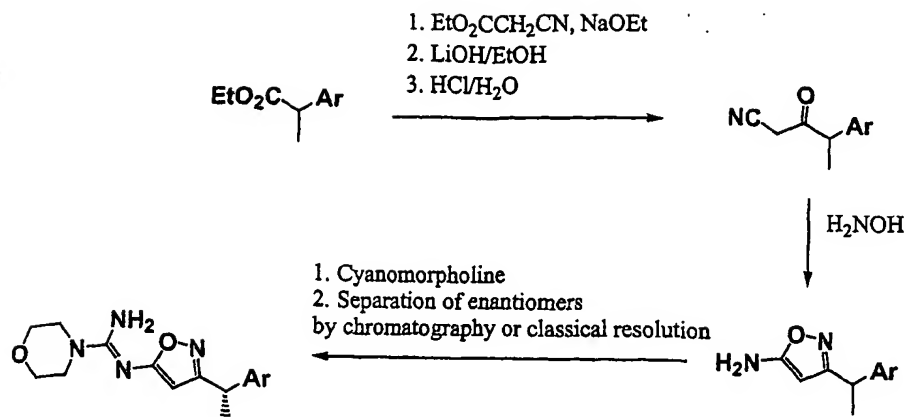
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Coupling of a suitable aniline **147.1** wherein X^1 is hydrogen, halo, trifluoromethyl, (C₁-C₃)alkyl, cyano, or (C₁-C₃)alkoxy, with acid chloride **147.2** provides a representative compound of the invention.

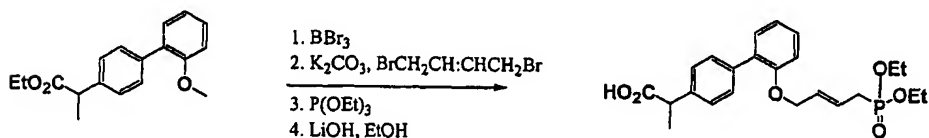
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Example 148 Synthesis of Representative Compounds of the Invention

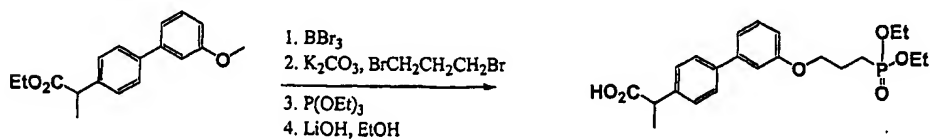


Compounds of the invention can be prepared as generally illustrated above. A β -ketonitrile is generated from a phenylacetic acid by condensation with a malononitrile ester under Claisen conditions. Reaction with hydroxylamine provides the 5-amino-1,2-oxazole which, upon condensation with cyanomorpholine provides a SMP-114 analog of the invention.

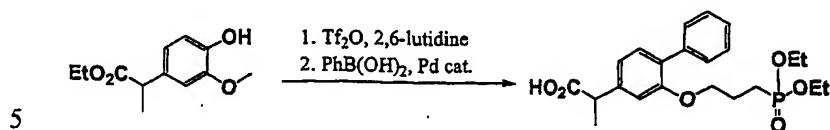
The preparation of suitable carboxylic acid intermediates that can be incorporated into the above synthetic scheme is detailed below.



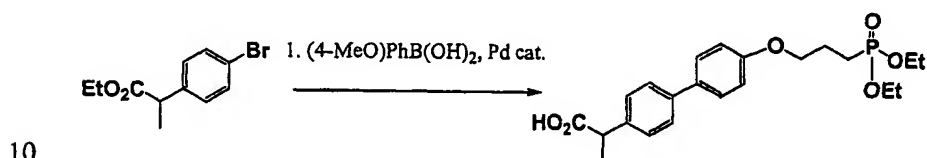
The anisole derivative is demethylated by treatment with a Lewis acid such as boron tribromide. The resulting phenol is alkylated with *E*-1,4-dibromobutene and the resulting monobromide is heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., Synthesis of carbon-phosphorus bonds, CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid. Saponification of the carboxylate ester gives the phenylacetic acid ready for incorporation into the synthesis of SMP-



Using a procedure similar to that described above, except replacing *E*-1,4-dibromobutene with 1,3-dibromopropane, a suitable intermediate can be prepared.



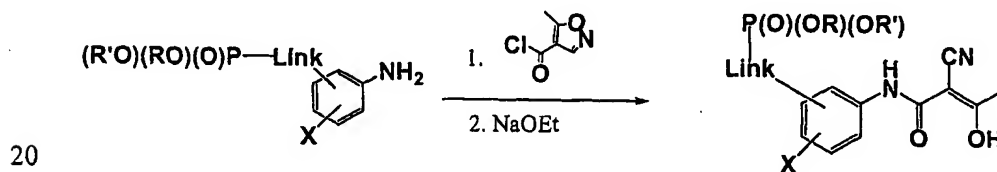
The free phenol in ethyl homovanillate is converted to the aryl triflate, and the biphenyl motif is generated by Suzuki coupling with phenylboronic acid (see *Chem. Rev.*, 1995, 95, 2457). The remaining steps are analogous to those described immediately above.



Ethyl 4-bromophenylacetate is coupled with 4-methoxyphenylboronic acid using the Suzuki method. The remaining steps are analogous to those described above.

15 Example 149 Synthesis of Representative Compounds of the Invention

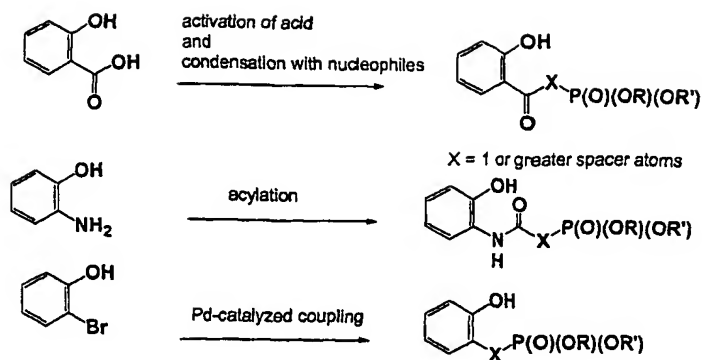
Compounds of the invention can be prepared as generally described by Westwood et al, *J. Med. Chem.*, 1996, 39, 4608-4621, according to the general route outline below.



Coupling of a suitable aniline wherein X is hydrogen, halo, trifluoromethyl, cyano, or methyl with acid chloride followed by treatment with sodium ethoxide provides a representative compounds of the invention.

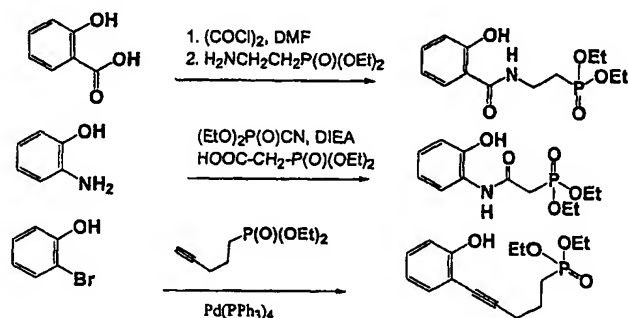
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Example 150 Synthesis of Representative Compounds of the Invention



Representative compounds of the invention can generally be prepared as

5 illustrated above.

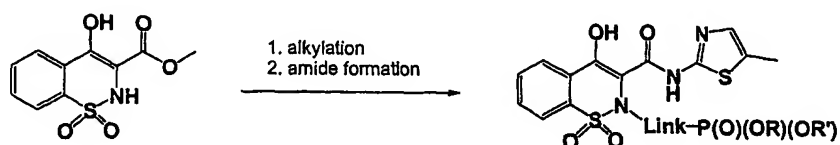


Certain specific salicylic acid analogs of the invention can be prepared as illustrated above. Salicylic acid is converted to its acid chloride by treatment with oxalyl chloride in dimethylformamide. The acid chloride is then coupled with 2-aminoethylphosphonic acid diethyl ester in the presence of a base such as triethylamine in a solvent such as dichloromethane to generate the desired amide product.

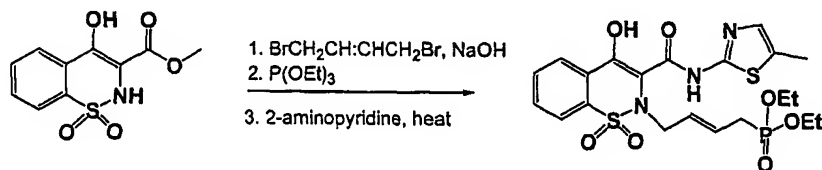
2-Aminophenol is acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, 1982, 25, 960-964 and *J. Med. Chem.*, 1984, 27, 600-604. The activated diethylphosphonoacetic acid is obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

2-Bromoaniline is coupled with pent-4-ynyl-phosphonic acid diethyl ester (generated from 5-chloro-1-pentyne and triethylphosphite in a solvent such as toluene, or other Arbuzov reaction conditions: see Engel, R., Synthesis of carbon-phosphorus bonds, CRC press, 1988) under conditions such as those pioneered by Sonogashira (Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, 1975, 4467) to afford the desired salicylic acid analog containing a phosphonate.

Example 151 Synthesis of Representative Compounds of the Invention

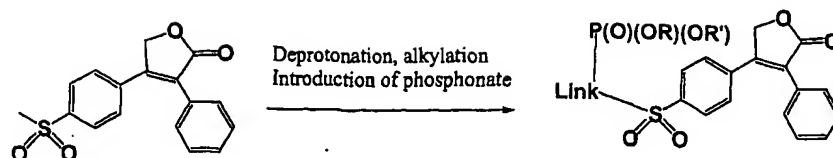


Compounds of the invention can generally be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.

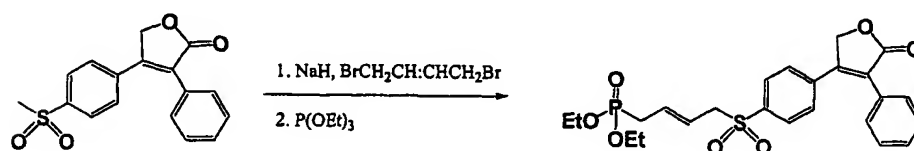


The methyl ester shown is treated in a solvent such as ethanol with excess *E*-1,4-dibromobutene in the presence of a base such as sodium hydroxide, as described in *J. Med. Chem.*, 1997, 40, 980. The monobromide so formed is then heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., Synthesis of carbon-phosphorus bonds, CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid. Finally, heating with 2-aminothiazole in solvents such as xylenes, as described in *J. Med. Chem.*, 1997, 40, 980, gives the desired meloxicam analogue.

Example 152 Synthesis of Representative Compounds of the Invention

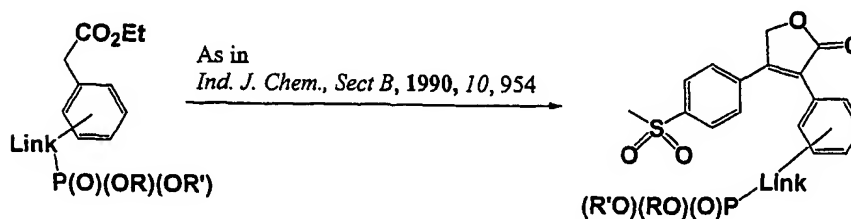


Compounds of the invention can generally be prepared as illustrated
 5 above. For example, a specific compound of the invention can be prepared as follows.

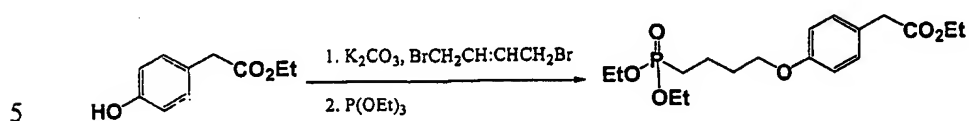


- 10 Rofecoxib is treated in a solvent such as dimethylformamide or tetrahydrofuran with a base such as sodium hydride. When bubbling ceases, *E*-1,4-dibromobutene is added in excess. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated product is isolated by chromatography.
- 15 The bromide so formed is heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., Synthesis of carbon-phosphorus bonds, CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid.

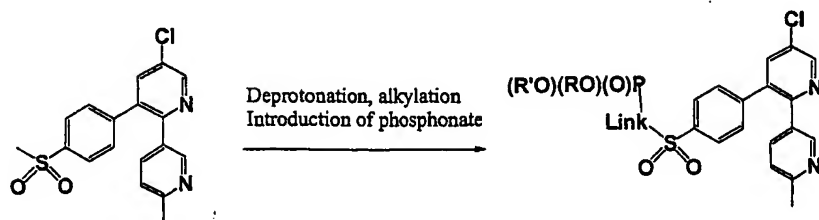
20 Example 153 Synthesis of Representative Compounds of the Invention



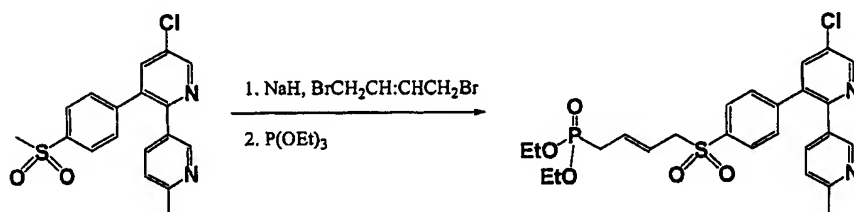
Compounds of the invention can generally be prepared as illustrated above (see also, *Ind. J. Chem., Sect B*, 1990, 10, 954.) A specific intermediate useful in the above process can be prepared as follows.



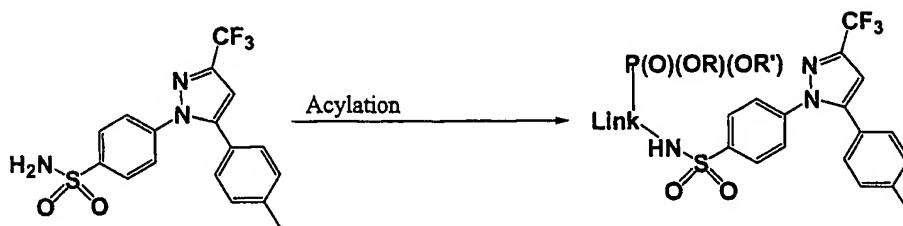
Ethyl 4-hydroxyphenylacetate is treated in a solvent such as dimethylformamide or tetrahydrofuran with a base such as sodium hydride. When bubbling ceases, *E*-1,4-dibromobutene is added in excess. After
10 quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated product is isolated by chromatography. The bromide so formed is heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., Synthesis of carbon-phosphorus bonds, CRC press,
15 1988) to generate the diethyl ester of the desired phosphonic acid.

Example 154 Synthesis of Representative Compounds of the Invention

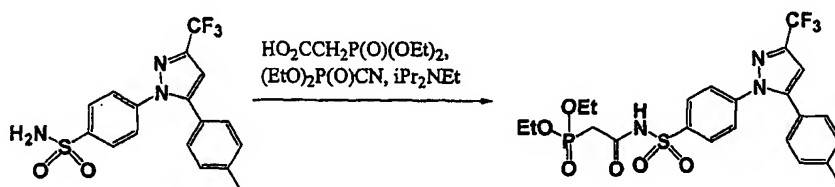
- 5 Compounds of the invention can generally be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.



- 10 Etoricoxib is treated in a solvent such as dimethylformamide or tetrahydrofuran with a base such as sodium hydride. When bubbling ceases, *E*-1,4-dibromobutene is added in excess. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated product is isolated by chromatography.
- 15 The bromide so formed is heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., Synthesis of carbon-phosphorus bonds, CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid.

20 Example 155 Synthesis of Representative Compounds of the Invention

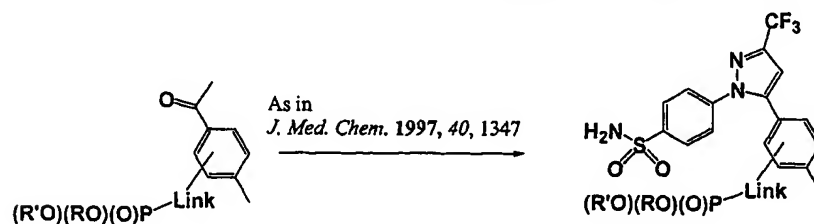
Compounds of the invention can generally be prepared as illustrated above. Acylation is achieved by reaction of the sulfonamide with an activated diethylphosphonoacetic acid to provide the desired compound, according to a procedure such as those reported in *J. Med. Chem.*, **1982**, *25*, 960 and *J. Med. Chem.*, **1984**, *27*, 600. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature. For example, a specific compound of the invention can be prepared as follows.



Acylation is achieved by reaction of the sulfonamide with an activated diethylphosphonoacetic acid to provide the desired compound, according to a procedure such as those reported in *J. Med. Chem.*, **1982**, *25*, 960 and *J. Med. Chem.*, **1984**, *27*, 600. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

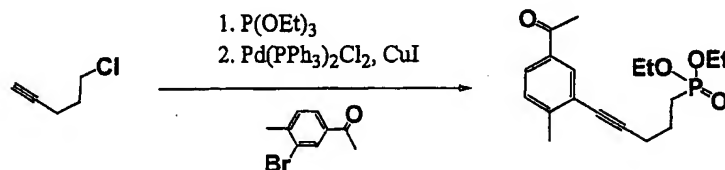
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Example 156 Synthesis of Representative Compounds of the Invention



Compounds of the invention can generally be prepared as illustrated above. The synthesis of celecoxib analogs from a number of acetophenones is

described in detail in *J. Med. Chem.*, **1997**, *40*, 1347. The synthesis of a suitable phosphonate-containing acetophenone is illustrated below.

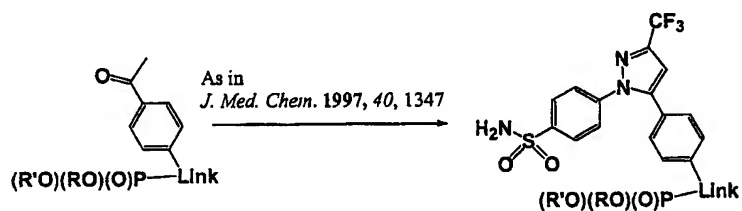


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5-Chloro-1-pentyne is treated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., *Synthesis of carbon-phosphorus bonds*, CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid. This acetylene is coupled with 3'-bromo-4-methylacetophenone under conditions such as those pioneered by Sonagashira (Sonagashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, **1975**, 4467).

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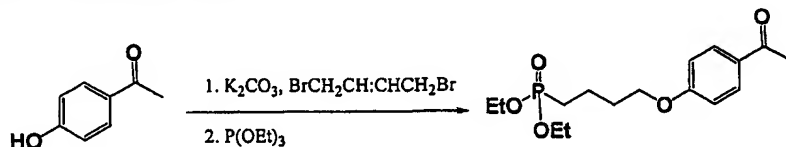
Example 157 Synthesis of Representative Compounds of the Invention



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Compounds of the invention can generally be prepared as illustrated above. The synthesis of celecoxib analogs from a number of acetophenones is described in detail in *J. Med. Chem.*, **1997**, *40*, 1347. The synthesis of a suitable acetophenone linked at the 4' position to a phosphonate moiety is illustrated below.

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4'-Hydroxyacetophenone is treated in a solvent such as dimethylformamide or tetrahydrofuran with a base such as sodium hydride.

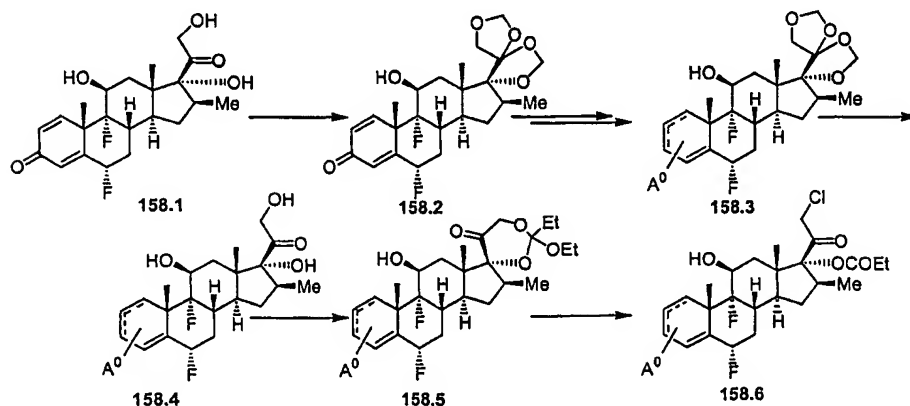
25 When bubbling ceases, *E*-1,4-dibromobutene is added in excess. After

quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated product is isolated by chromatography. The bromide so formed is heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., Synthesis of carbon-phosphorus bonds, CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid.

Examples 158-161 Preparation of Halobetasol Derivatives

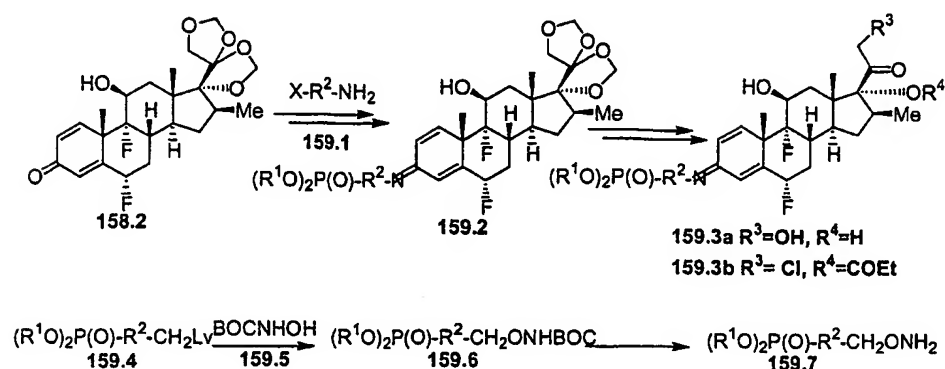
The synthesis of representative phosphonate derivatives of halobetasol is outlined in Examples 158-161. In these Examples, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The protection and deprotection of steroidal ketones and alcohols is described in Organic Reactions in Steroid Chemistry, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

Example 158 Preparation of Representative Halobetasol Derivatives



The preparation of representative compounds of the invention is illustrated above. The steroid side-chain is protected as a bis-methylenedioxy (BMD) moiety. In this sequence, 6 α ,9 α -difluoro-16 β -methyl-11 β ,17 α ,21-trihydroxypregn-1,4-dien-3,21-dione **158.1** (US Patent 4,619,921) is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to yield the BMD derivative **158.2**. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester **158.3**. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to afford the triol **158.4**. The latter compound is then converted into the 17,21-cyclic orthoester **158.5** using the procedure described in *Chem. Pharm. Bull.*, 1986, 34, 1613. The substrate is reacted in dimethylformamide at 70°C with two molar equivalents of triethyl orthopropionate and a catalytic amount of p-toluenesulfonic acid. The product is then reacted with an excess of trimethylsilyl chloride in dimethylformamide at ambient temperature to produce the 21-chloro 17-propionate product **158.6**.

Alternatively, the substrate **158.4** is converted into the product **158.6** by means of the method described in *J. Med. Chem.*, (1987), 30: 1581. In this procedure, the 21-hydroxy group is activated by conversion to the 21-mesylate, by reaction with mesyl chloride in pyridine; the mesylate group is then displaced to yield the 21-chloro intermediate, by reaction with lithium chloride in dimethylformamide, and the 17-hydroxyl group is esterified to give the 21-chloro-17-propionate derivative **158.6**. The selective acylation of the 17 α hydroxyl group in the presence of an 11 β hydroxyl group is described in *J. Med. Chem.*, (1987), 30: 1581.

Example 159 Preparation of Representative Halobetasol Derivatives

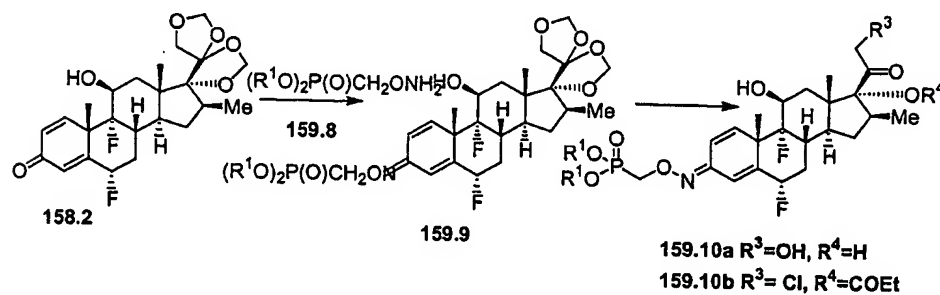
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The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the BMD-protected derivative 158.2 is reacted with an amine or hydroxylamine 159.1, in which R² is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example,

X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, (1978), 86, 133. and in *J. Mass. Spectrom.*, (1995), 30, 497. The BMD-protected side-chain compound 159.2 is then converted into the triol 159.3a, and then to the 21-chloro 17 propionate product 159.3b.

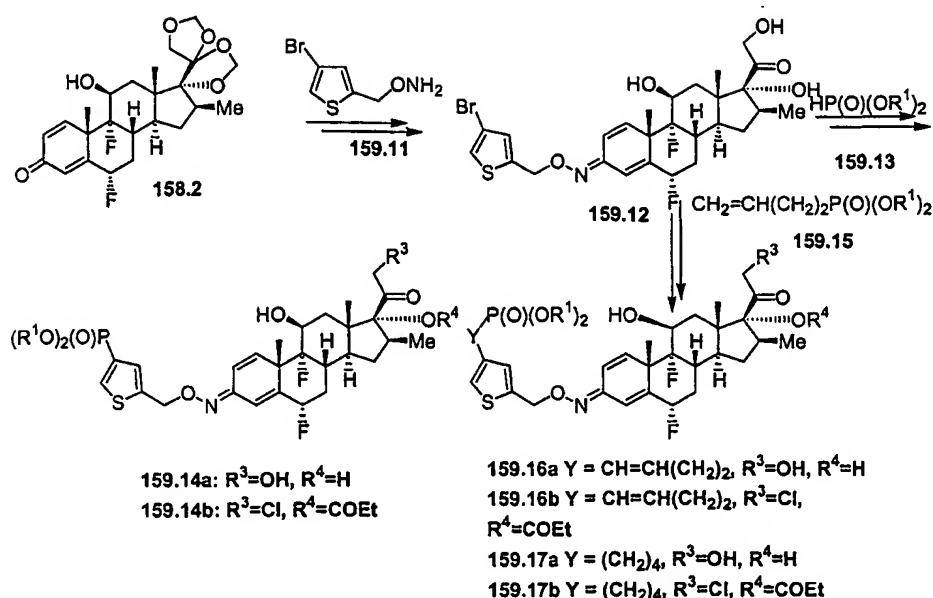
The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated above. In this procedure, a phosphonate 159.4, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine 159.5 (Aldrich) to produce the ether 159.6. The

reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether 159.7.



The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate **158.2** is reacted with a dialkyl phosphonomethyl hydroxylamine **159.8**, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tet. Lett.* 27:1477 (1986)) and BOC-hydroxylamine, to afford the oxime **159.9**. Deprotection then affords the triol **159.10a** from which the 21-chloro 17-propionate compound **159.10b** is prepared. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether **159.8**, different oxime ethers **159.1**, the corresponding products **159.3b** are obtained.



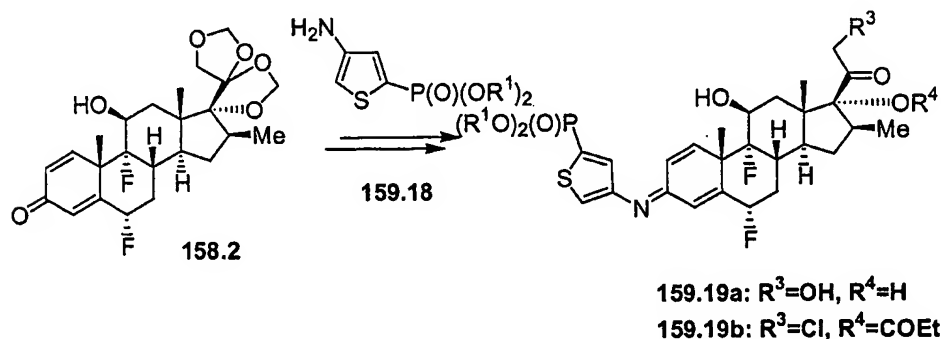
- The preparation of compounds in which the phosphonate group is
- 5 attached by means of a thienylmethoxy oxime group is illustrated above. In this procedure, the dienone **158.2** is reacted, as described above, with O-(4-bromo-2-thienylmethoxy)hydroxylamine **159.11**, prepared as described above from 4-bromo-2-bromomethylthiophene (WO 9420456) and BOC-protected hydroxylamine, to give, after deprotection of the side-chain, the oxime **159.12**.
- 10 The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **159.13** to afford the phosphonate **159.14a**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.* 35:1371 (1992). The reaction is performed in an inert solvent such as toluene, in the presence of a base such as
- 15 triethylamine and a catalytic amount of tetrakis(triphenylphosphine)-palladium(0). The 21-hydroxy compound **159.14a** is then converted into the 21-chloro 17-propionate derivative **159.14b**.

Alternatively, the bromo compound **159.12** is coupled with a dialkyl butenyl phosphonate **159.15** (*Org. Lett.* 3:217 (2001)) to afford the phosphonate

20 **159.16a**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry* 503ff (Plenum, 2001) and in *Acc. Chem. Res.* 12:146 (1979). The aryl

bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the double bond present in the product **159.16a** is reduced, for example by reaction with diimide, to produce the saturated analog **159.17a**. The reduction of olefinic bonds is described in R. C. Larock, Comprehensive Organic Transformations 6ff (VCH 1989). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane. The products **159.16a** and **159.17a** are then converted into the 21-chloro 17-propionate analogs **159.16b** and **159.17b**.

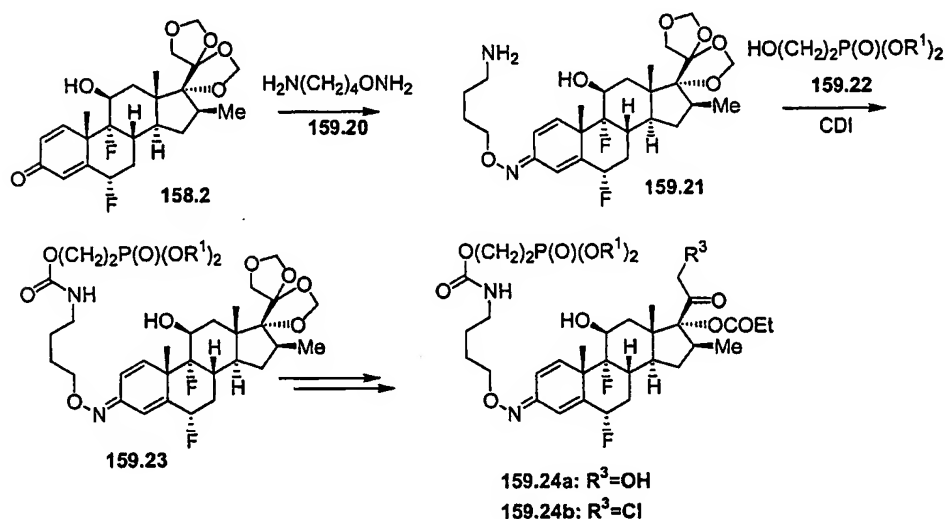
Using the above procedures, but employing, in place of the bromothiénylmethoxy reagent **159.11**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds **159.14b**, **159.16b** and **159.17b** are obtained.



The preparation of representative phosphonates of the invention is illustrated above. In this procedure, the substrate **158.2** is reacted with a dialkyl 4-amino-2-thienyl phosphonate **159.18**, prepared by the palladium-catalyzed coupling, as described above, between 4-amino-2-bromothiophene (*Tet.* 43:3295 (1987)) and a dialkyl phosphite, to give, after deprotection, the imine product **159.19a**. The imine forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid,

under azeotropic conditions. The product is then converted into the 21-chloro 17-propionate compound **159.19b**.

Using the above procedures, but employing, in place of the 4-aminothienyl phosphonate **159.18** different amino-substituted aryl or heteroaryl phosphonates, products analogous to **159.19b** are obtained.



The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and an amide linkage is illustrated above. In this procedure, the dienone **158.2** is reacted with O-(4-aminobutyl)hydroxylamine **159.20** (*Pol. J. Chem.* 55:1163 (1981)) to yield the oxime **159.21**. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.* 7:795 (1976); the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product is then coupled with a dialkyl 2-hydroxyethyl phosphonate **159.22** (Epsilon) and carbonyl diimidazole, to yield the carbamate oxime **159.23**. The preparation of carbamates is described in A. R. Katritzky, *Comprehensive Organic Functional Group Transformations*, 6:416ff (Pergamon, 1995), and in S. R. Sandler and W. Karo, *Organic Functional Group Preparations*, 260ff (Academic Press, 1986). In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent

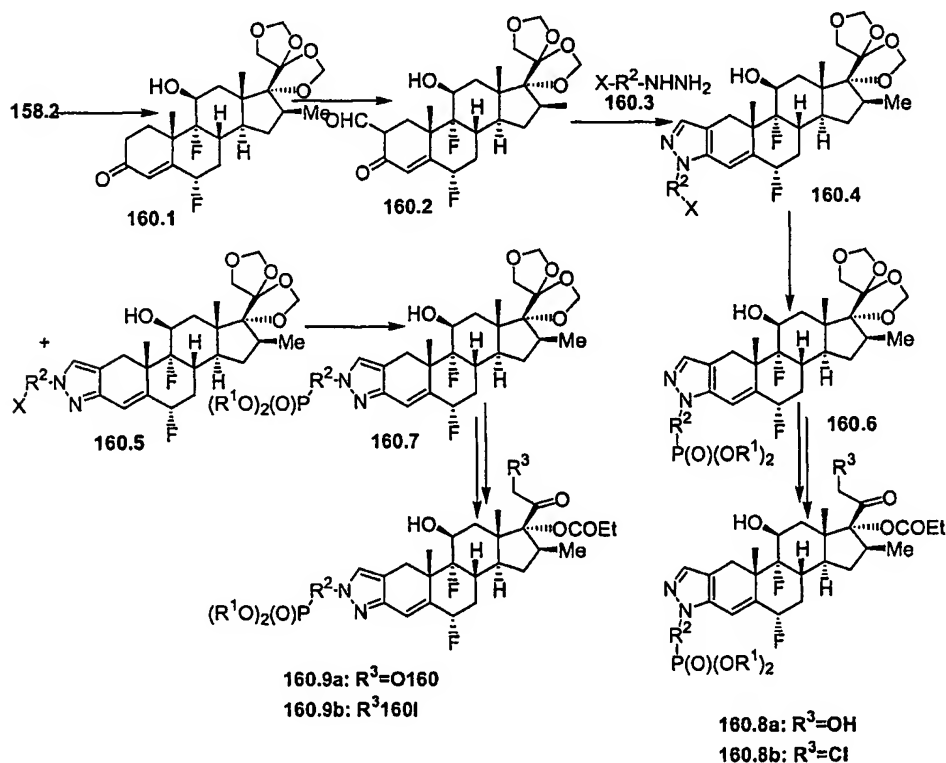
thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate. The carbamate product **159.23** is then converted into the 21-chloro 17-propionate product

5 **159.24b.**

Using the above procedures, but employing, in place of the hydroxylamine **159.22**, different amino-substituted hydroxylamines, and/or different hydroxy-substituted phosphonates, the products analogous to **159.24b** are obtained.

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Example 160 Preparation of Representative Halobetasol Derivatives



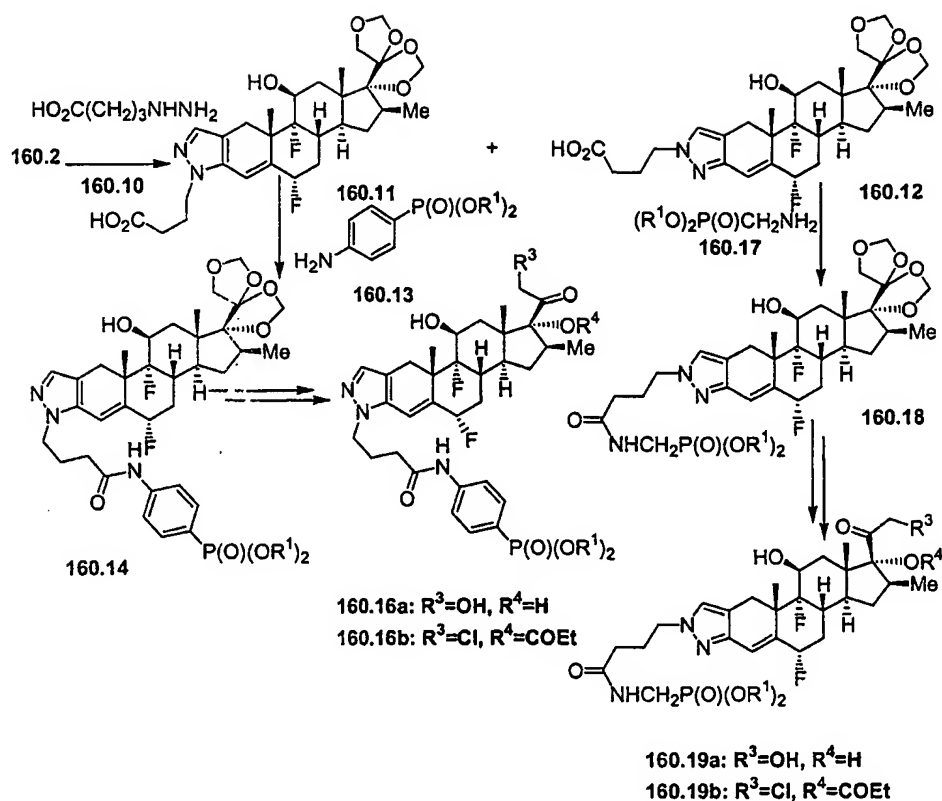
15 The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and/or a variable carbon chain is illustrated above. In this procedure, the BMD-protected dienone **158.2** is

reduced to afford the 1,2-dihydro product **160.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.* 44:602 (2001). The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent

5 such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.* 86:1520 (1964), to afford the 2-formyl product **160.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine **160.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is

10 dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles **160.4** and **160.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.* 86:1520 (1964). The pyrazoles **160.4** and **160.5** are then transformed via the BMD-

15 protected intermediates **160.6** and **160.7**, into the 21-chloro 17-propionate phosphonates **160.8b** and **160.9b**.



The preparation of phosphonates in which the phosphonate is attached by means of an amide linkage is illustrated above. In this procedure, the ketoaldehyde **160.2** is reacted, as described above, with 3-carboxypropyl hydrazine **160.10** (*Ind. J. Exp. Biol.* 32:218 (1994)) to give the pyrazoles **160.11** and **160.12**. The 2'-substituted isomer **160.11** is then reacted in dimethylformamide solution at ambient temperature with one molar equivalent of a dialkyl 4-aminophenyl phosphonate **160.13** (Epsilon) and dicyclohexyl carbodiimide, to yield the amide **160.14**. The preparation of amides from carboxylic acids and derivatives is described, for example, in S.R.Sandler and W. Karo, *Organic Functional Group Preparations*, 274 (Academic Press, 1968), and R. C. Larock, *Comprehensive Organic Transformations*, 972ff (VCH, 1989). The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone; in a non-

protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

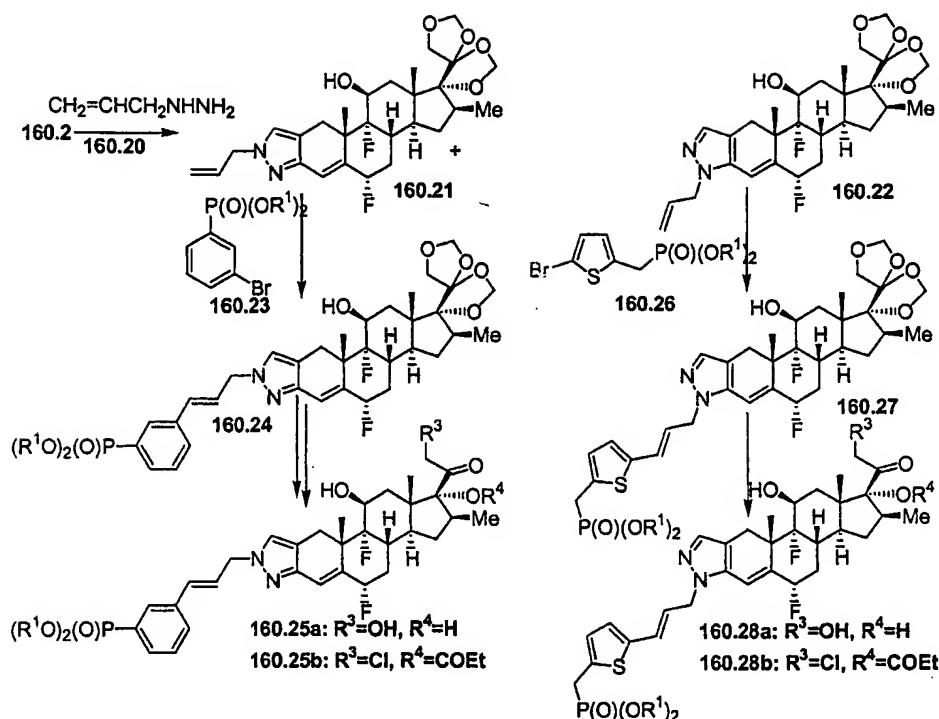
Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide
5 and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as
10 dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

The BMD protecting group is then removed and the product is converted into the 21-chloro 17-propionate product **160.16b**.

Alternatively, the 1'-substituted pyrazole **160.12** is coupled, as described
15 above, with a dialkyl aminomethyl phosphonate **160.17** (Interchim), to afford the amide **160.18**. The product **160.18** is then deprotected to give the triol **160.19a**, and the latter compound is transformed into the 21-chloro 17-propionate **160.19b**.

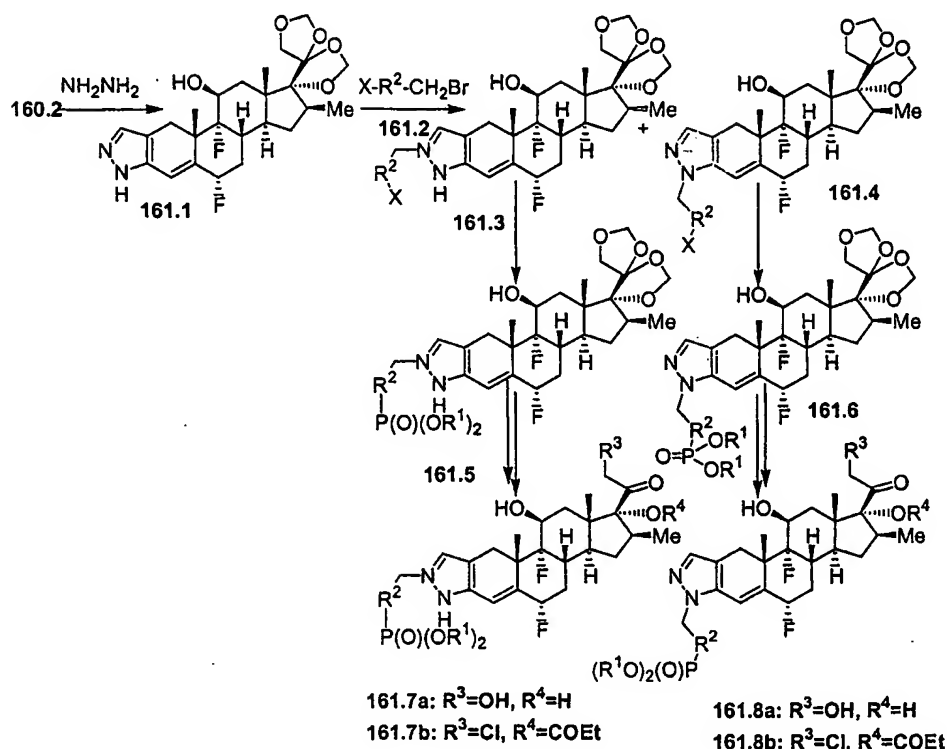
Using the above procedures, but employing different amino-substituted
20 phosphonates, and/or different carboxy-substituted hydrazines, the products analogous to **160.16b** and **160.19b** are obtained. The functionalization procedures are interchangeable between the pyrazole substrates **160.11** and **160.12**.



The preparation of the phosphonates in which the phosphonate group is attached by means of an aryl ring and a propenyl linkage is illustrated above. In this procedure, the ketoaldehyde **160.2** is reacted, as described above, with allylhydrazine **160.20** (*Zh. Org. Khim.*, 3:983 (1967)) to produce the pyrazoles **160.21** and **160.22**. The 1'-substituted isomer **160.21** is coupled with a dialkyl 3-bromophenyl phosphonate **160.23** (Epsilon) to give the phosphonate **160.24**. The product is then deprotected to afford the triol **160.25a** which is converted into the 21-chloro 17-propionate compound **160.25b**.

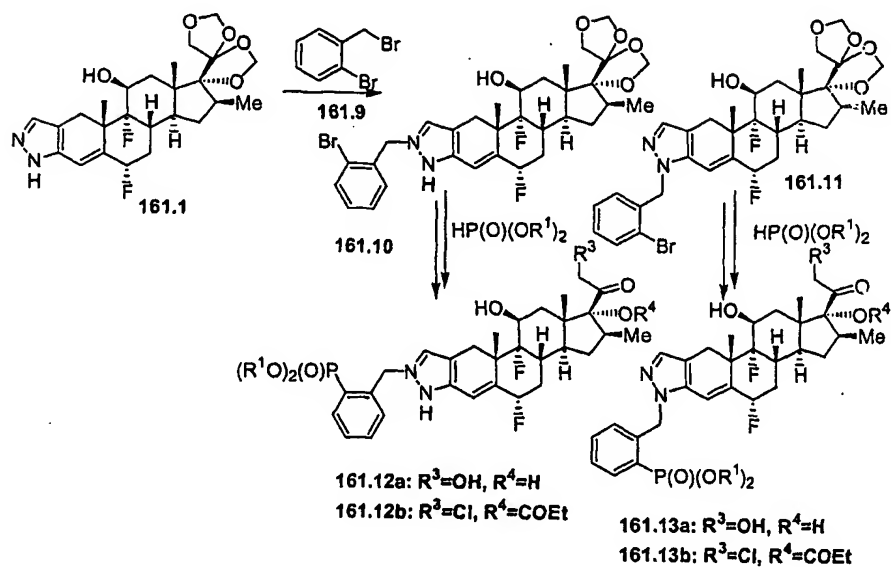
Alternatively, the 2'-substituted pyrazole **160.22** is coupled, as described above, with a dialkyl 5-bromo-2-thienyl phosphonate **160.26** (*Syn.*, 455 (2003)) to prepare the phosphonate **160.27** which is deprotected, and the product is converted into the 21-chloro 17-propionate analog **160.28b**.

Using the above procedures, but employing, in place of the propenyl hydrazine **160.20**, different alkenyl hydrazines, and/or different dialkyl bromo-substituted phosphonates, the products analogous to the compounds **160.25b** and **160.28b** are obtained.

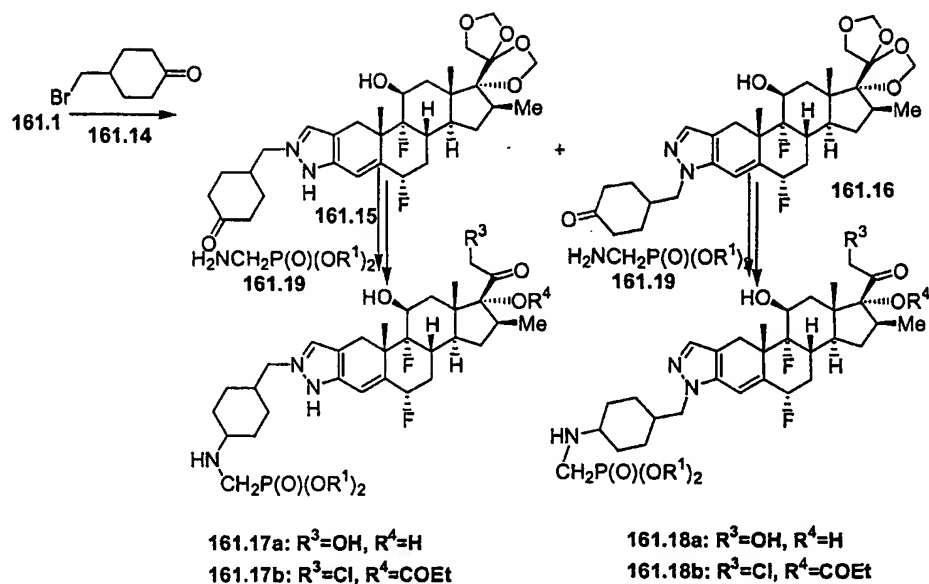
Example 161 Preparation of Representative Halobetasol Derivatives

- 5 The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde **160.2** is reacted with hydrazine, to afford the pyrazole derivative **161.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, 86:1520 (1964). The reaction is
- 10 performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound **161.2**, in which R^2 and X are as defined above, to yield the alkylation products **161.3** and **161.4**. The alkylation of substituted pyrazoles is described, for example, in T. L. Gilchrist, *Heterocyclic Chemistry*, 309 (Longman, 1992). The reaction is performed between equimolar
- 15 amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products **161.3** and **161.4** are, except in cases where X is dialkylphosphono, converted into the phosphonates **161.5** and **161.6**, using the procedures described herein, and

deprotection/chlorination/acylation then affords the 21-chloro 17-propionate compounds **161.7b** and **161.8b**.



- 5 Representative compounds of the invention can be prepared as illustrated above. The pyrazole **161.1** is reacted with 2-bromobenzyl bromide **161.9** to give the pyrazoles **161.10** and **161.11**. The products are then coupled, as described above, with a dialkyl phosphite, to afford after side-chain deprotection and modification, as described above, the 21-chloro 17 propionates **161.12b** and
- 10 **161.13b**.



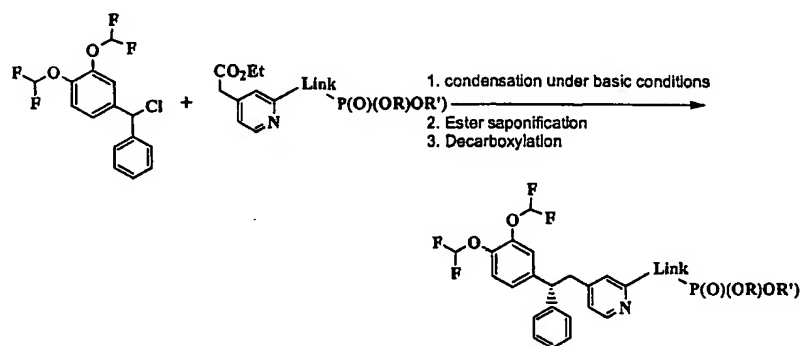
Representative compounds of the invention can be prepared as illustrated above. The pyrazole **161.1** is reacted in tetrahydrofuran solution, as described above, with 4-bromomethyl cyclohexanone **161.14** (WO 9737959) to give the alkylation products **161.15** and **161.16**. The 1'-substituted isomer **161.15** is then reacted, in a reductive amination reaction, with a dialkyl aminomethyl phosphonate (Interchim) and sodium cyanoborohydride, to yield, after deprotection and side-chain modification, the 21-chloro 17-propionate **161.17b**.

The preparation of amines by means of reductive amination procedures is described, for example, in R. C. Larock, *Comprehensive Organic Transformations*, 421 (VCH, 1989), and in F.A. Carey and R. J. Sundberg, *Advanced Organic Chemistry, Part B*, 269 (Plenum, 2001). In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in *J. Org. Chem.*, 55:2552 (1990).

The 2'-substituted pyrazole **161.16** is subjected to the same series of reaction to give the amine phosphonate **161.18b**.

Using the above procedures, but employing different bromomethyl-substituted aldehydes or ketones, and/or different amino-substituted phosphonates, the products analogous to 161.17b and 161.18b are obtained.

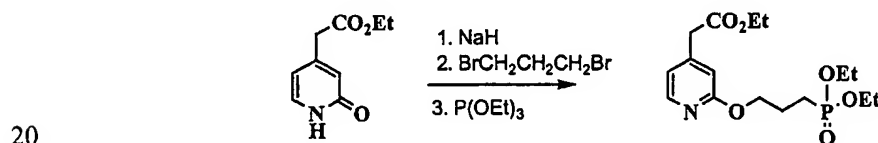
5 Example 162 Synthesis of Representative Compounds of the Invention



link includes 1 or more atoms; 2 or more is preferred

Compounds of the invention can generally be prepared as illustrated above. The chloride is made from (3,4-bis-difluoromethoxy-phenyl)-phenyl-methanone (cf US 5,622,977) by reduction with sodium borohydride in ethanol and treatment of the resulting alcohol with triphenylphosphine, carbon tetrachloride and diisopropyl azodicarboxylate in a solvent such as tetrahydrofuran. The condensation is achieved by treatment of the two reagents with sodium ethoxide in ethanol. The ethyl ester in the product is saponified by treatment with lithium hydroxide in ethanol, and the resulting acid is decarboxylated by heating under acidic conditions. The two enantiomers of the product may be separated by chromatography.

For example, a specific pyridine reagent can be prepared as follows.



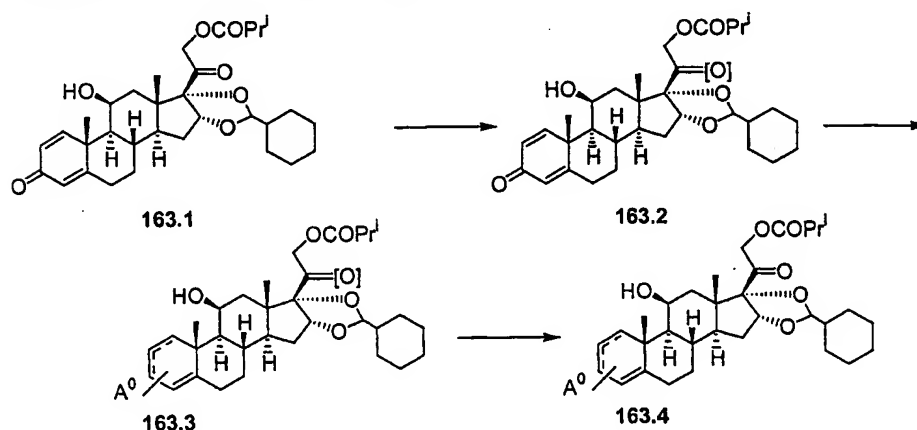
(2-Oxo-1,2-dihydro-pyridin-4-yl)-acetic acid ethyl ester is treated with a base such as sodium hydride in a solvent such as tetrahydrofuran. After

bubbling ceases, an excess of 1,3-dibromopropane is added. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-bromide is isolated by chromatography. The bromide is then heated with triethylphosphite in a solvent
 5 such as toluene to generate the diethyl ester of the desired phosphonic acid.

Examples 163-166 Ciclesonide Derivatives

The synthesis of representative phosphonate derivatives of ciclesonide is outlined in Examples 166-169. In these Examples, it may be necessary to
 10 protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The
 15 protection and deprotection of steroidal ketones and alcohols is described in Organic Reactions in Steroid Chemistry, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

Example 163 Preparation of Representative Ciclesonide Derivatives



Representative compounds of the invention can be prepared as follows.

25 Ciclesonide 163.1 (US Patent No. 5482934) is protected to afford the derivative

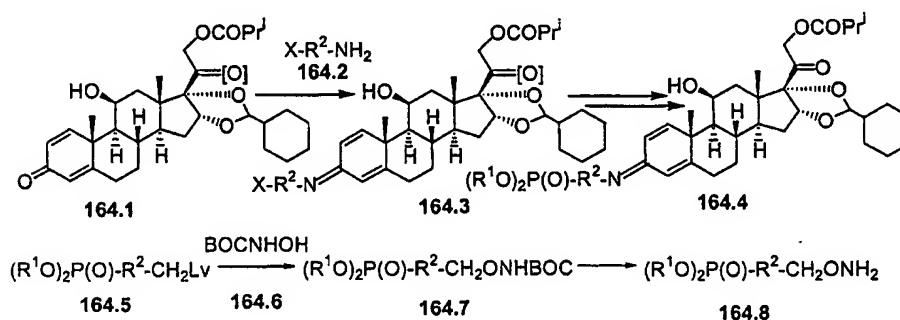
163.2. The ketone is protected, for example, by conversion to the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, 77:1904 (1955). Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in *J. Chem. Soc. Chem. Comm.* 1351 (1987).

Alternatively, the 20-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone 163.1 with N,N-dimethylhydrazine in ethanol-acetic acid, as described in *Org. Syn.* 50:102 (1970). The group is removed by treatment with sodium acetate and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.* 101:5841 (1979).

Alternatively, the 20-ketone is protected as the diethylamine adduct. In this procedure, the substrate 163.1 is reacted with titanium tetrakis(diethylamide), as described in *J. Chem. Soc. Chem. Comm.* 406 (1983), to afford the adduct. The ketone is deprotected by reaction with water in an aqueous organic solvent.

The protected compound 163.2 is then converted into the phosphonate-containing analog 163.3, using the procedures described below, and the protecting group is then removed, as described above, to give the phosphonate 163.4.

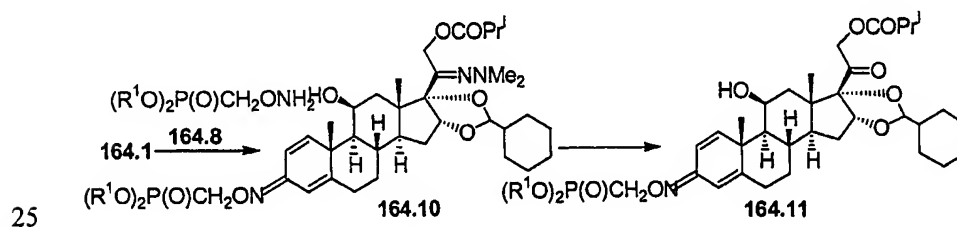
Example 164 Preparation of Representative Ciclesonide Derivatives



The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the protected derivative 164.1 is reacted with an amine

or hydroxylamine **164.2**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime **164.3**. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.* 86:133 (1978) and in *J. Mass. Spectrom.* 30:497 (1995). The protecting group is then removed to afford the 20-keto phosphonate product **164.4**.

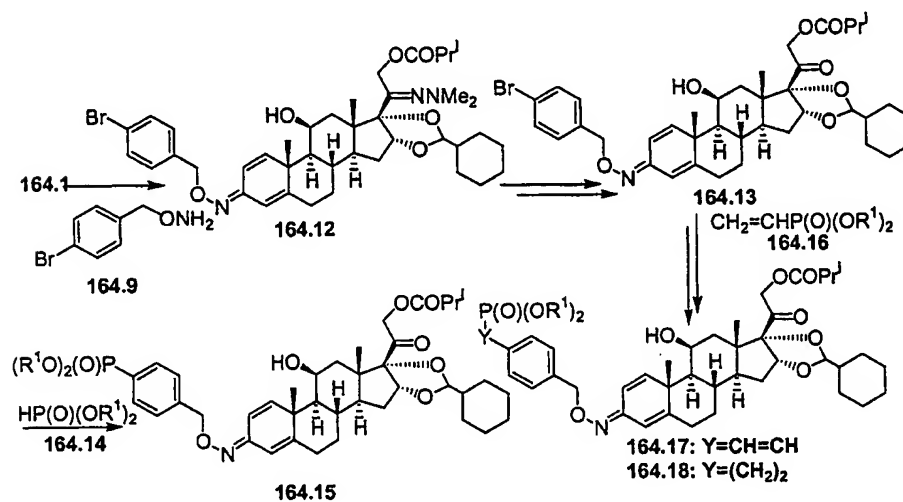
The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated above. In this procedure, a phosphonate **164.5**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine **164.6** (Aldrich) to produce the ether **164.7**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether **164.8**. The above procedure is also employed for the preparation of substituted hydroxylamines which are precursors to phosphonates.



The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate **164.1**, in which the 20-ketone is protected as the dimethyl hydrazone derivative, is reacted with a dialkyl phosphonomethyl hydroxylamine **164.8**, prepared as

described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tetrahedron Lett.* 27:1477 (1986)) and BOC-hydroxylamine, to afford the oxime **164.10**. Deprotection affords the 20-keto phosphonate **164.11**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether **164.8**, different oxime ethers **164.2**, the corresponding products **164.4** are obtained.



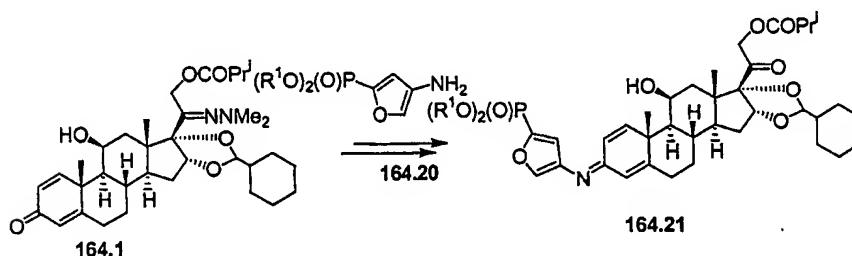
10

The preparation of compounds in which the phosphonate group is attached by means of a benzyloxy oxime group is illustrated above. In this procedure, the dienone **164.1**, in which the 20-ketone is protected as the dimethyl hydrazone, is reacted, as described above, with O-(4-bromobenzoyloxy)hydroxylamine **164.9**, prepared as described above from 4-bromobenzyl bromide and BOC-protected hydroxylamine **164.6**, to give the oxime **164.12**. The protecting group is then removed to yield the 20-keto product **164.13**. The latter product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **164.14** to afford the phosphonate **164.15**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.* 35:1371 (1992). The reaction is performed at ca. 100°C in an inert solvent such as toluene, in the

presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Alternatively, the bromo compound **164.13** is coupled with a dialkyl vinyl phosphonate **164.16** (Aldrich) to afford the phosphonate **164.17**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, Advanced Organic Chemistry 503ff (Plenum, 2001) and in *Acc. Chem. Res.* 12:146 (1979). The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product **164.17** is reduced, for example by reaction with diimide, to produce the saturated analog **164.18**. The reduction of olefinic bonds is described in R. C. Larock, Comprehensive Organic Transformations 6ff (VCH 1989). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromobenzoyloxy reagent **164.9**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, products analogous to the compounds **164.15**, **164.17** and **164.18** are obtained.



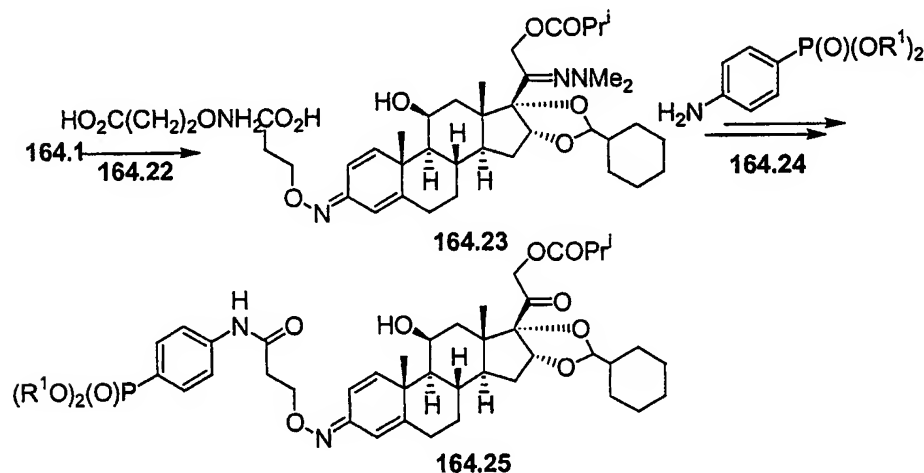
The preparation of phosphonates in which the phosphonate is attached by means of a 3-furylimino group is illustrated above. In this procedure, the substrate **164.1**, in which the 20-ketone is protected as the dimethylhydrazone, is

reacted with a dialkyl 4-amino-2-furyl phosphonate **164.20**, prepared by the palladium catalyzed coupling reaction, as described above, between 4-amino-2-bromofuran (*Tetrahedron Lett.* 43:3295 (1987)) and a dialkyl phosphite, to give, after deprotection, the imine product **164.21**. The imine forming reaction is

5 conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions.

Using the above procedures, but employing, in place of the 4-amino-2-furyl phosphonate **164.20** different amino-substituted aryl or heteroaryl phosphonates, products analogous to **164.21** are obtained.

10 phosphonates, products analogous to **164.21** are obtained.



The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and an amide linkage is illustrated above. In this

15 procedure, the dienone **164.1**, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with O-(2-carboxyethyl)hydroxylamine **164.22** (*J. Med. Chem.* 33:1423 (1990)) to yield the oxime **164.23**. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.* 7:795 (1976); the reaction is performed between equimolar

20 amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product **164.23** is then coupled with a dialkyl 4-aminophenyl phosphonate **164.24** (Epsilon) and dicyclohexylcarbodiimide, to yield, after deprotection the amide oxime **164.25**. The preparation of amides from carboxylic acids and derivatives is described, for

example, in S.R.Sandler and W. Karo, *Organic Functional Group Preparations* 274 (Academic Press, 1968) and R. C. Larock, Comprehensive Organic Transformations 972ff (VCH, 1989). The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example,

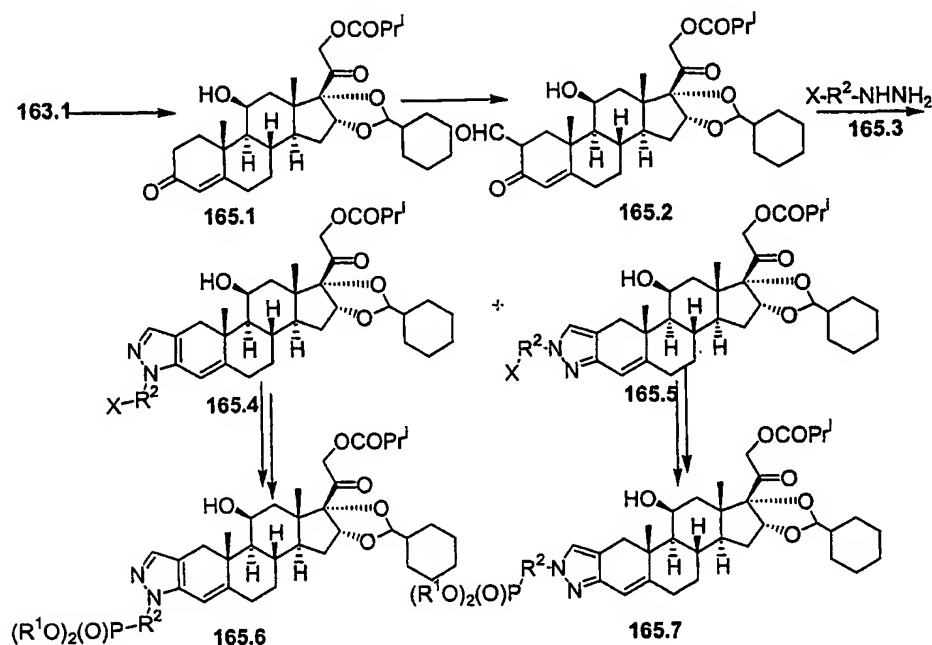
5 dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenzotriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated
10 derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

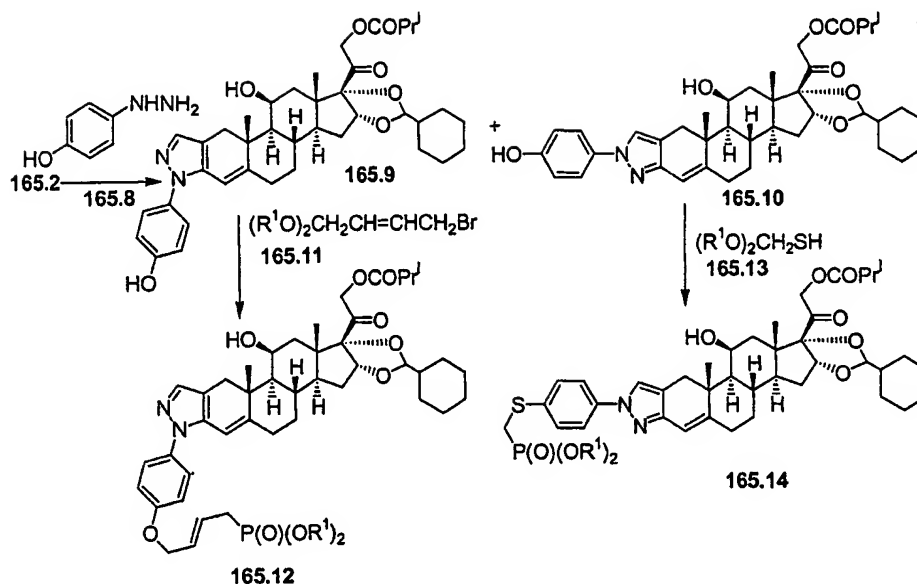
The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for
15 example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

Using the above procedures, but employing, in place of the carboxy-substituted hydroxylamine 164.22, different carboxy-substituted
20 hydroxylamines, and/or different amino-substituted phosphonates, products analogous to 164.25 are obtained.

Example 165 Preparation of Representative Ciclesonide Derivatives



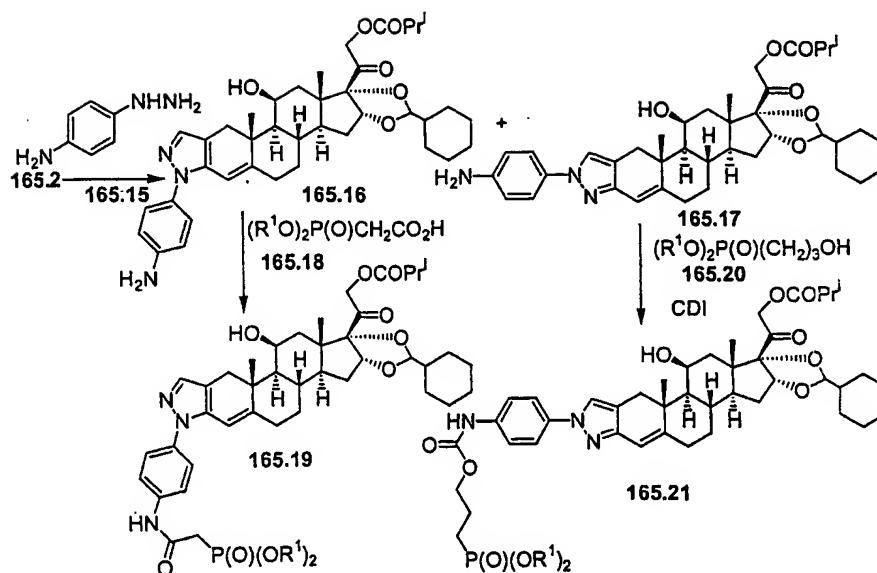
- The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and/or a variable carbon chain is illustrated above. In this procedure, the dienone **163.1** is reduced to afford the 1,2-dihydro product **165.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.* 44:602 (2001). The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.* 86:1520 (1964), to afford the 2-formyl product **165.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine **165.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles **165.4** and **165.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.* 86:1520 (1964). The pyrazoles **165.4** and **165.5** are then transformed into the phosphonates **165.6** and **165.7**.



The preparation of phosphonates in which the phosphonate is attached by means of an alkoxy or alkylthio linkage is illustrated above. In this procedure, the ketoaldehyde 165.2 is reacted, as described above, with 4-hydroxyphenylhydrazine 165.8 (EP 437105) to give the pyrazoles 165.9 and 165.10. The 2'-substituted isomer 165.9 is then reacted in dimethylformamide solution at ca. 70°C with a dialkyl bromobutenyl phosphonate 165.11 (*J. Med. Chem.* 35:1371 (1992)) and potassium carbonate, to yield the ether phosphonate 165.12.

The isomeric pyrazole 165.10 is reacted, in a Mitsunobu reaction, with a dialkyl mercaptomethyl phosphonate 165.13 (*J. Med. Chem.* 26:1688 (1985)) to yield the thioether phosphonate 165.14. The preparation of aromatic ethers and thioethers by means of the Mitsunobu reaction is described, for example, in R. C. Larock, *Comprehensive Organic Transformations* 448 (VCH, 1989), in F.A. Carey and R. J. Sundberg, *Advanced Organic Chemistry, Part B* 153-4 (Plenum, 2001), and in *Org. React.* 42:335 (1992). The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.* 42:335-656 (1992).

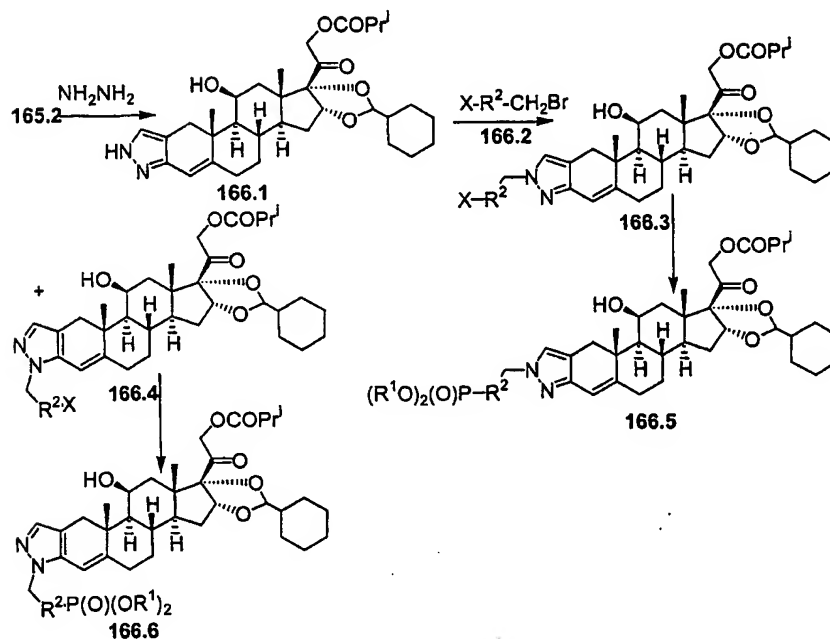
Using the above procedures, but employing different hydroxy-substituted hydrazines, and/or different bromo- or mercapto-substituted phosphonates, products analogous to 165.12 and 165.14 are obtained.



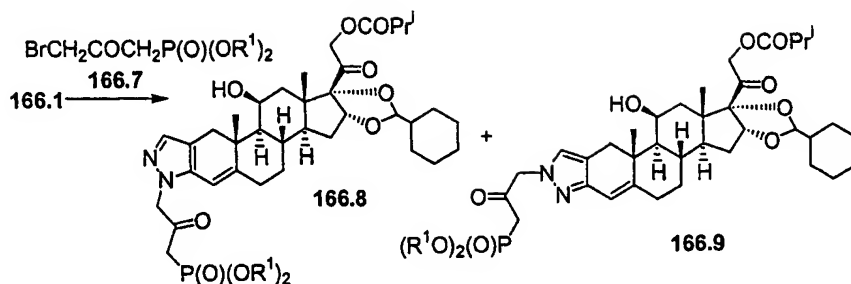
The preparation of the phosphonates in which the phosphonate group is attached by means of a phenyl group and an amide or carbamate linkage is illustrated above. In this procedure, the ketoaldehyde **165.2** is reacted, as described above, with 4-aminophenyl hydrazine **165.15** (Epsilon) to produce the pyrazoles **165.16** and **165.17**. The 2'-substituted isomer **165.16** is coupled, as described above, with a dialkyl phosphonoacetic acid **165.18** (Aldrich) and dicyclohexyl carbodiimide, to give the amide phosphonate **165.19**.

Alternatively, the 1'-substituted pyrazole **165.17** is reacted with a dialkyl 3-hydroxypropyl phosphonate **165.20** (*Zh. Obshchei. Khim.* 43:2364 (1973)), and carbonyl diimidazole to prepare the carbamate phosphonate **165.21**. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations Vol. 6 416ff (A. R. Katritzky, ed., Pergamon, 1995) and in S. R. Sandler and W. Karo, Organic Functional Group Preparations 260ff (Academic Press, 1986). In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate.

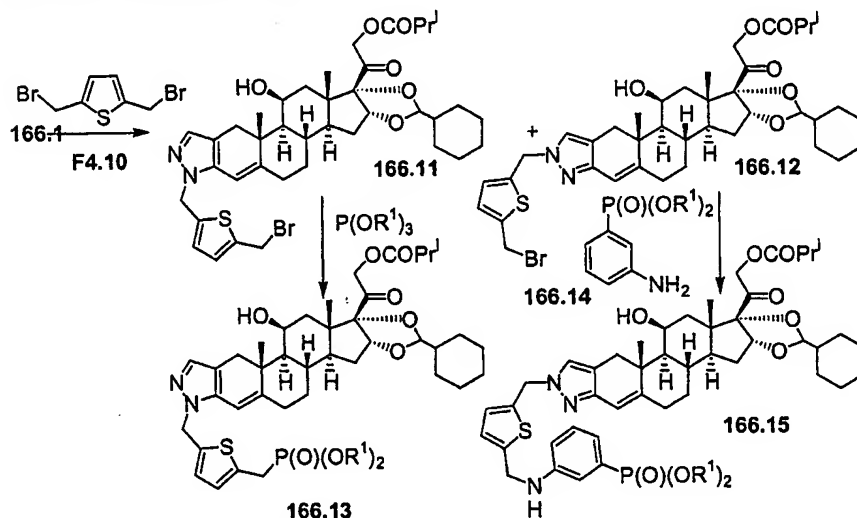
Using the above procedures, but employing, in place of the 4-aminophenyl hydrazine **165.15**, different amino-substituted hydrazines, and/or different dialkyl carboxy or hydroxy-substituted phosphonates, products analogous to the compounds **165.19** and **165.21** are obtained.

Example 166 Preparation of Representative Ciclesonide Derivatives

- The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde **165.2** is reacted with hydrazine, to afford the pyrazole derivative **166.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.* 86:1520 (1964). The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then
- reacted with a bromomethyl compound **166.2**, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products **166.3** and **166.4**. The alkylation of substituted pyrazoles is described, for example, in T. L. Gilchrist, *Heterocyclic Chemistry* 309 (Longman, 1992). The reaction is performed between equimolar amounts of the substrates in a
- polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products **166.3** and **166.4** are, except in cases where X is dialkylphosphono, converted into the phosphonates **166.5** and **166.6**, using the procedures described herein.



Representative compounds of the invention can be prepared as illustrated above. The pyrazole **166.1** is reacted, as described above, with a dialkyl
 5 acetonyl phosphonate **166.7** (*Tetrahedron Lett.* 34:649 (1978)) to give the pyrazoles **166.8** and **166.9**.



Representative compounds of the invention can be prepared as illustrated above. The pyrazole **166.1** is reacted in tetrahydrofuran solution, with 2,5-
 10 bis(bromomethyl)thiophene **166.10** (*Tetrahedron Lett.* 55:4709 (1999)) and potassium hexamethyl disilazide, to give the alkylation products **166.11** and **166.12**. The 2'-substituted isomer **166.11** is then reacted, in a Arbuzov reaction, with a trialkyl phosphite to yield the phosphonate **166.13**. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.* 115 (1992). In this procedure,
 15 in which a bromo substituent is converted into the corresponding phosphonate, the substrate is heated at from about 60°C to about 160°C with a five to fifty-fold molar excess of a trialkyl phosphite, to effect the transformation.

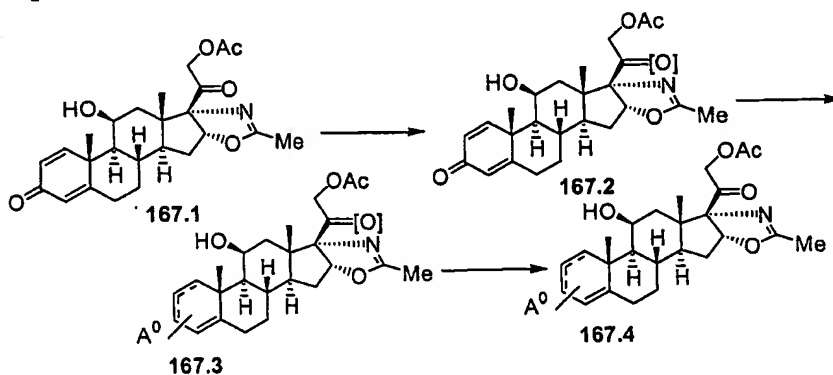
The 2'-substituted pyrazole **166.14** is reacted at 70°C in dimethylformamide solution with one molar equivalent of a dialkyl 3-aminophenyl phosphonate **166.14** and cesium carbonate, to give the amine phosphonate **166.15**.

- 5 Using the above procedures, but employing different dibromides, and/or different amino-substituted phosphonates, products analogous to **166.13** and **166.15** are obtained.

Examples 167-170 Deflazacort Derivatives

- 10 The synthesis of representative phosphonate derivatives of deflazacort is outlined in Examples 167-170. In these Examples, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic
15 of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The protection and deprotection of steroidal ketones and alcohols is described in Organic Reactions in Steroid Chemistry, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be
20 protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

Example 167 Preparation of Representative Deflazacort Derivatives



- 25 Representative compounds of the invention can be prepared as illustrated above. Deflazacort **167.1** (US Patent No. 3436389) is protected to afford the

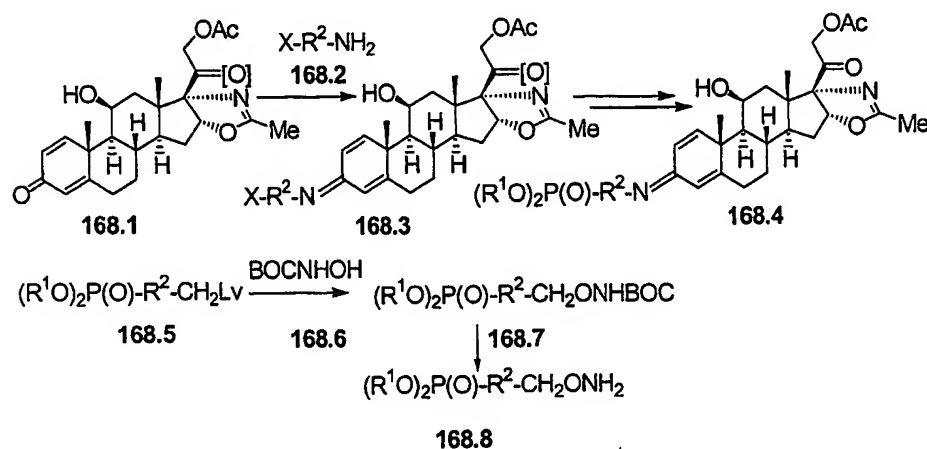
derivative **167.2**. The ketone is protected, for example, by conversion to the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, 77:1904 (1955). Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in *J. Chem. Soc. Chem. Comm.* 1351 (1987).

Alternatively, the 20-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone **167.1** with N,N-dimethylhydrazine in ethanol-acetic acid, as described in *Org. Syn.* 50:102 (1970). The group is removed by treatment with sodium acetate and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.* 101:5841 (1979).

Alternatively, the 20-ketone is protected as the diethylamine adduct. In this procedure, the substrate **167.1** is reacted with titanium tetrakis-(diethylamide), as described in *J. Chem. Soc. Chem. Comm.* 406 (1983), to afford the adduct. The ketone is deprotected by reaction with water in an aqueous organic solvent.

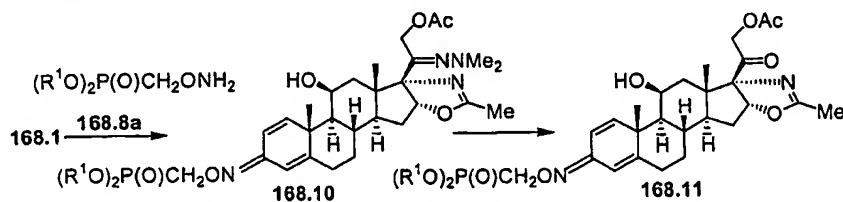
The protected compound **167.2** is then converted into the phosphonate-containing analog **167.3**, using the procedures described below, and the protecting group is then removed, as described above, to give the phosphonate **167.4**.

Example 168 Preparation of Representative Deflazacort Derivatives



The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain as illustrated above. In this procedure, the protected derivative **168.1** is reacted with an amine or hydroxylamine **168.2**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime **168.3**. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.* 86:133 (1978) and in *J. Mass. Spectrom.* 30:497 (1995). The protecting group is then removed to afford the 20-keto phosphonate product **168.4**.

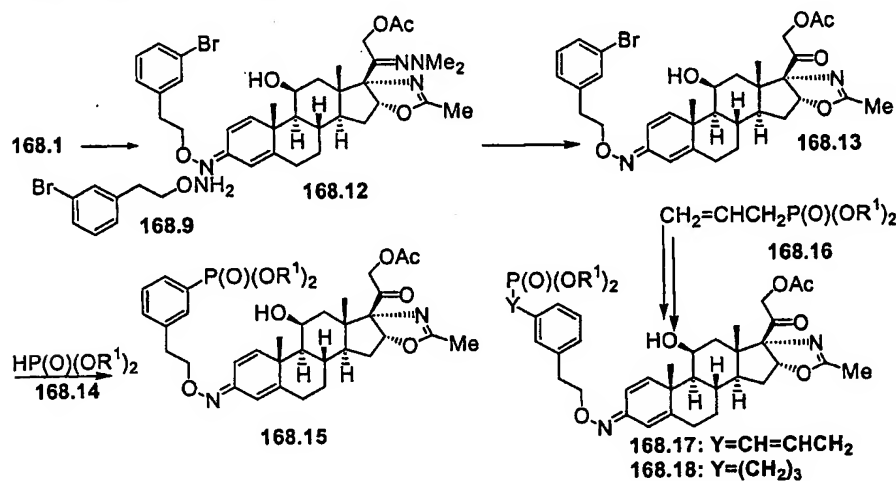
The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated. In this procedure, a phosphonate **168.5**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine **168.6** (Aldrich) to produce the ether **168.7**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether **168.8**. The above procedure is also employed for the preparation of substituted hydroxylamines which are precursors to phosphonates.



The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group as illustrated above. In this procedure, the substrate **168.1**, in which the 20-ketone is protected as the dimethyl hydrazone derivative,

is reacted with a dialkyl phosphonomethyl hydroxylamine **168.8a**, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tetrahedron Lett.* 27:1477 (1986)) and BOC-hydroxylamine, to afford the oxime **168.10**. Deprotection then affords the 20-keto phosphonate **168.11**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether **168.8a**, different oxime ethers **168.2**, the corresponding products **168.4** are obtained.



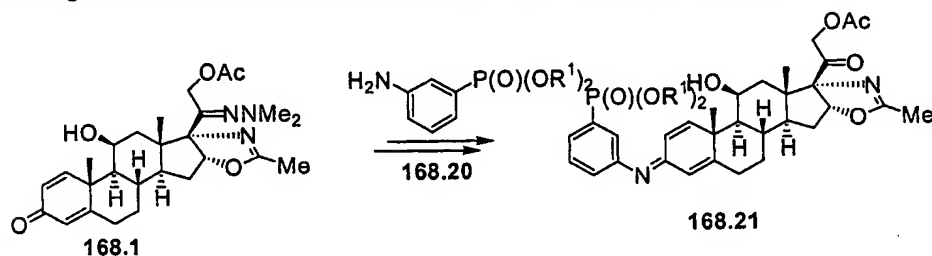
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The preparation of compounds in which the phosphonate group is attached by means of a phenylethoxy oxime group as illustrated above. In this procedure, the dienone **168.1**, in which the 20-ketone is protected as the dimethyl hydrazone, is reacted, as described above, with O-(3-bromophenylethoxy)hydroxylamine **168.9**, prepared as described above from 3-bromophenylethyl bromide (French Patent FR 1481052), and BOC-protected hydroxylamine **168.6**, to give the oxime **168.12**. The protecting group is then removed to yield the 20-keto product **168.13**. The latter product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **168.14** to afford the phosphonate **168.15**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.* 35:1371 (1992). The reaction is performed at ca. 100°C in an

inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Alternatively, the bromo compound 168.13 is coupled with a dialkyl propenyl phosphonate 168.16 (Aldrich) to afford the phosphonate 168.17. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry* 503ff (Plenum, 2001) and in *Acc. Chem. Res.* 12:146 (1979). The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product 168.17 is reduced, for example by reaction with diimide, to produce the saturated analog 168.18. The reduction of olefinic bonds is described in R. C. Larock, *Comprehensive Organic Transformations* 6ff (VCH 1989). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

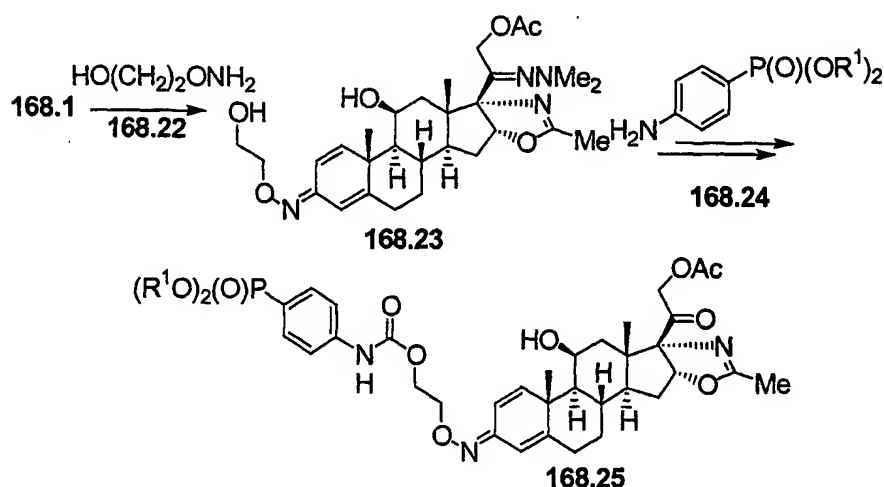
Using the above procedures, but employing, in place of the bromophenylethyl reagent 168.9, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, products analogous to the compounds 168.15, 168.17 and 168.18 are obtained.



The preparation of phosphonates in which the phosphonate is attached by means of a 3-phenylimino group as illustrated above. In this procedure, the substrate 168.1, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with a dialkyl 3-aminophenyl phosphonate 168.20 (*J. Med. Chem.* 27:654 (1984)), to give, after deprotection, the imine product 168.21. The imine

forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions.

- 5 Using the above procedures, but employing, in place of the 3-aminophenyl phosphonate 168.20 different amino-substituted aryl or heteroaryl phosphonates, products analogous to 168.21 are obtained.



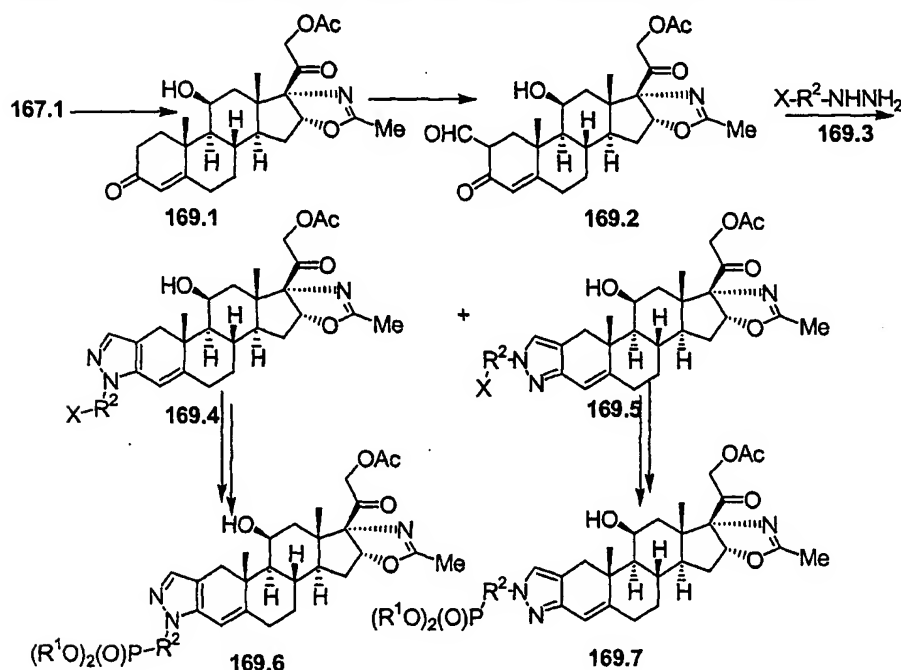
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- The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and a carbamate linkage as illustrated above. In this procedure, the dienone 168.1, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with O-(2-hydroxyethyl)hydroxylamine 168.22 (*J. Chem. Soc. Chem. Comm.* 903 (1986)) to yield the oxime 168.23. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.* 7:795 (1976); the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product 168.23 is then coupled with a dialkyl 4-aminophenyl phosphonate 168.24 (Epsilon) and carbonyl diimidazole, to yield, after deprotection, the carbamate oxime 168.25. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations Vol. 6 416ff (A. R. Katritzky, ed., Pergamon, 1995) and in S. R. Sandler and W. Karo, Organic Functional Group Preparations
- 15
- 20

260ff (Academic Press, 1986). In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate.

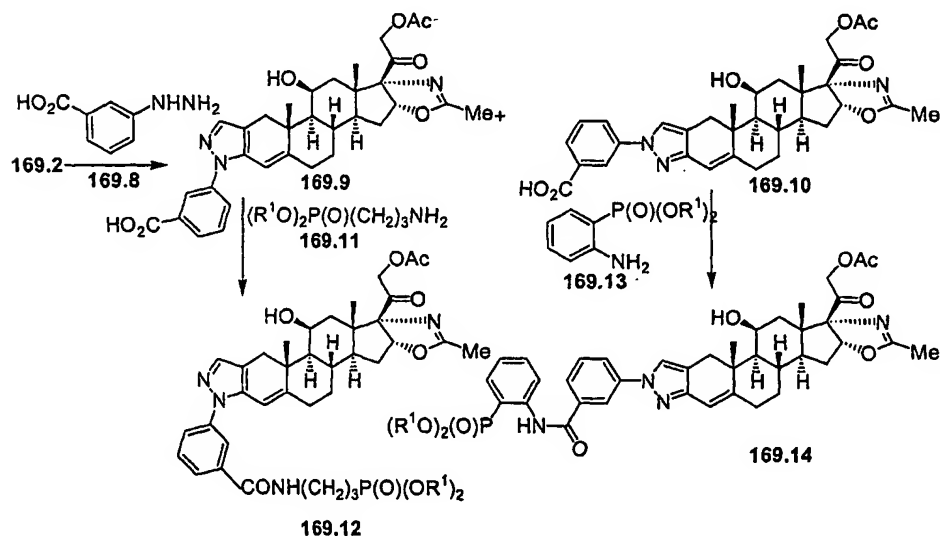
Using the above procedures, but employing, in place of the hydroxy-substituted hydroxylamine **168.22**, different hydroxy-substituted hydroxylamines, and/or different amino-substituted phosphonates, the products analogous to **168.25** are obtained.

Example 169 Preparation of Representative Deflazacort Derivatives



The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and/or a variable carbon chain as illustrated above. In this procedure, the dienone **167.1** is reduced to afford the 1,2-dihydro product **169.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example, as described in *J. Med. Chem.* 44:602 (2001). The product is then reacted with

ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.* 86:1520 (1964), to afford the 2-formyl product **169.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine **169.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles **169.4** and **169.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.* 86:1520 (1964). The pyrazoles **169.4** and **169.5** are then transformed into the phosphonates **169.6** and **169.7**.



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The preparation of phosphonates in which the phosphonate is attached by means of an amide linkage is illustrated above. In this procedure, the ketoaldehyde **169.2** is reacted, as described above, with 3-carboxyphenylhydrazine **169.8** (Apin) to give the pyrazoles **169.9** and **169.10**. The 2'-substituted isomer **169.9** is then coupled in dimethylformamide solution at ambient temperature with a dialkyl 3-aminopropyl phosphonate **169.11** (Acros) and dicyclohexyl carbodiimide, to yield the amide phosphonate **169.12**. The preparation of amides from carboxylic acids and derivatives is described, for

example, in S.R.Sandler and W. Karo, Organic Functional Group Preparations 274 (Academic Press, 1986), and R. C. Larock, Comprehensive Organic Transformations 972ff (VCH, 1989). The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example,

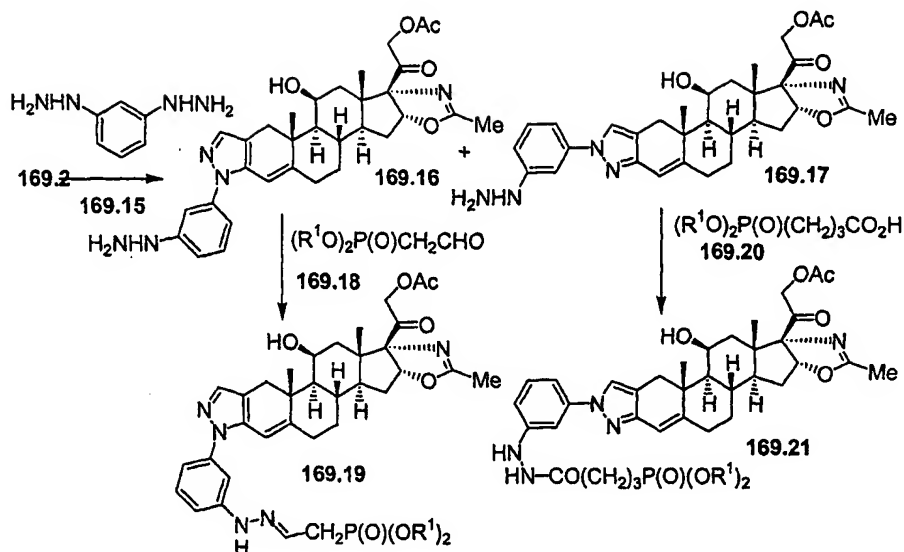
5 dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated
10 derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for
15 example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

The isomeric pyrazole **169.10** is reacted, as described above, with a dialkyl 2-aminophenyl phosphonate **169.13** (Acros) to yield the amide
20 phosphonate **169.14**.

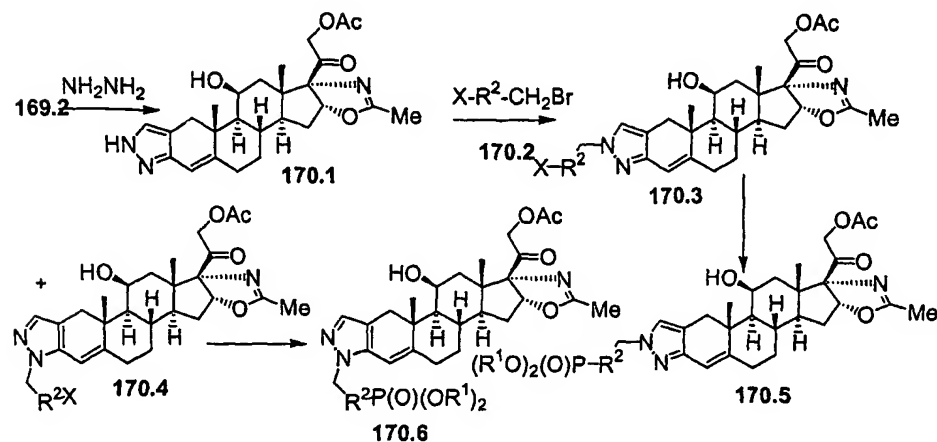
Using the above procedures, but employing different carboxy-substituted hydrazines, and/or different amino-substituted phosphonates, the products analogous to **169.12** and **169.14** are obtained.



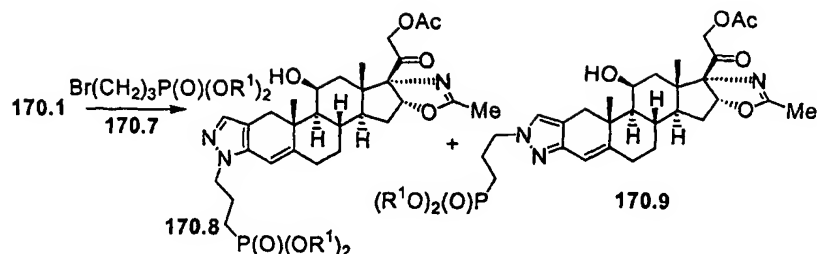
The preparation of the phosphonates in which the phosphonate group is attached by means of a phenyl group and a hydrazone or acyl hydrazine linkage is illustrated above. In this procedure, the ketoaldehyde 169.2 is reacted, as described above, with 1,3-bis(hydrazino)benzene 169.15 (*Bull. Soc. Chim. Fr.* 1371 (1975)) to produce the pyrazoles 169.16 and 169.17. The 2'-substituted isomer 169.16 is reacted in tetrahydrofuran solution at ambient temperature with one molar equivalent of a dialkylphosphono acetaldehyde (Aurora), to give the hydrazone phosphonate 169.19.

Alternatively, the 1'-substituted pyrazole 169.17 is coupled, as described above, with a dialkylphosphono butyric acid 169.20 (Epsilon) and dicyclohexyl carbodiimide to prepare the phosphonate 169.21.

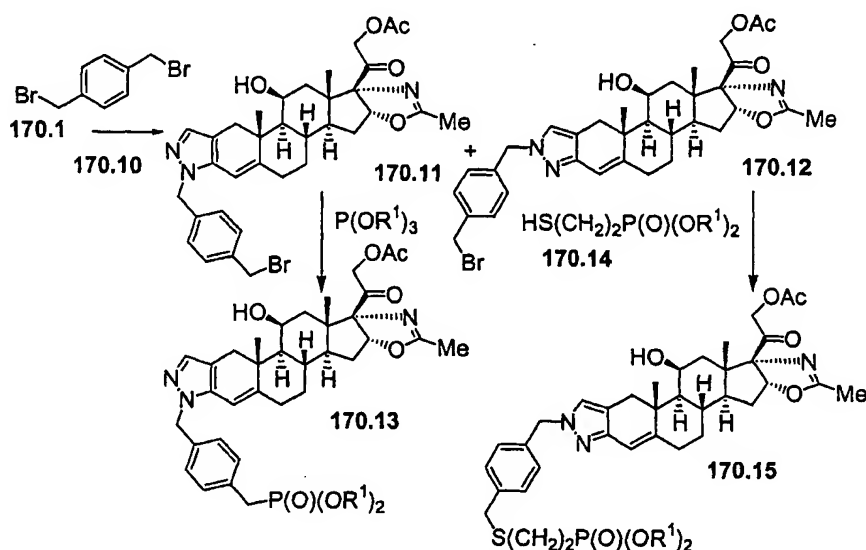
Using the above procedures, but employing, in place of the 1,3-bis(hydrazino)phenyl hydrazine 169.15, different bis hydrazines, and/or different dialkyl formyl or carboxy-substituted phosphonates, the products analogous to the compounds 169.19 and 169.21 are obtained.

Example 170 Preparation of Representative Deflazacort Derivatives

- 5 The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage as illustrated above. In this procedure, the ketoaldehyde **169.2** is reacted with hydrazine to afford the pyrazole derivative **170.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.* 86:1520 (1964). The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then
- 10 reacted with a bromomethyl compound **170.2**, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products **170.3** and **170.4**. The alkylation of substituted pyrazoles is described, for example, in T. L. Gilchrist, *Heterocyclic Chemistry* 309 (Longman, 1992).
- 15 The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products **170.3** and **170.4** are, except in cases where X is dialkylphosphono, converted into the phosphonates **170.5** and **170.6**, using the procedures described
- 20 herein.



- Representative compounds of the invention can be prepared as illustrated above. The pyrazole 170.1 is reacted in dimethylformamide solution at 70°C with one molar equivalent of a dialkyl bromopropyl phosphonate 170.7
- 5 (Synthelec) and cesium carbonate, to give the pyrazoles 170.8 and 170.9.



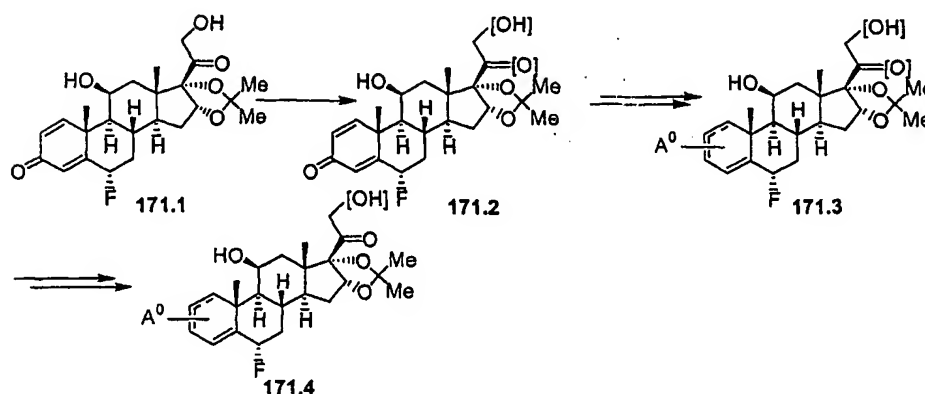
- Representative compounds of the invention can be prepared as illustrated above. the pyrazole 170.1 is reacted in tetrahydrofuran solution with 1,4-
- 10 bis(bromomethyl)benzene 170.10 and potassium hexamethyl disilazide, to give the alkylation products 170.11 and 170.12. The 2'-substituted isomer 170.11 is then reacted, in an Arbuzov reaction, with a trialkyl phosphite to yield the phosphonate 170.13. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.* 115 (1992). In this procedure, in which a bromo
- 15 substituent is converted into the corresponding phosphonate, the substrate is heated at from about 60°C to about 160°C with a five to fifty-fold molar excess of a trialkyl phosphite, to effect the transformation.

The 2'-substituted pyrazole **170.14** is reacted at 70°C in dimethylformamide solution with one molar equivalent of a dialkyl mercaptoethyl phosphonate **170.14** (*Zh. Obschei. Khim.* 43:2364 (1973)) and cesium carbonate, to give the thioether phosphonate **170.15**.

- 5 Using the above procedures, but employing different dibromides, and/or different mercapto-substituted phosphonates, products analogous to **170.13** and **170.15** are obtained.

Examples 171-174 Flunisolid Derivatives

- 10 The synthesis of representative phosphonate derivatives of Flunisolid is outlined in Examples 171-174. In these Examples, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in *Protective Groups in Organic*
- 15 *Synthesis*, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The protection and deprotection of steroidal ketones and alcohols is described in *Organic Reactions in Steroid Chemistry*, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be
- 20 protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

Example 171 Preparation of Representative Flunisolide Derivatives

5

Representative compounds of the invention can be prepared as illustrated above. The 20-ketone group and/or the 21-hydroxyl group of Flunisolide 171.1 (US Patent No. 3124571) are protected to afford the derivative 171.2. The ketone is protected, for example, by conversion to the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, 77:1904 (1955). Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in *J. Chem. Soc. Chem. Comm.* 1351 (1987).

Alternatively, the 20-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone 171.1 with N,N-dimethylhydrazine in ethanol-acetic acid, as described in *Org. Syn.* 50:102 (1970). The group is removed by treatment with sodium acetate and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.* 101:5841 (1979).

Alternatively, the 20-ketone is protected as the diethylamine adduct. In this procedure, the substrate 171.1 is reacted with titanium tetrakis(diethylamide), as described in *J. Chem. Soc. Chem. Comm.* 406 (1983), to afford the adduct. The ketone is deprotected by reaction with water in an aqueous organic solvent.

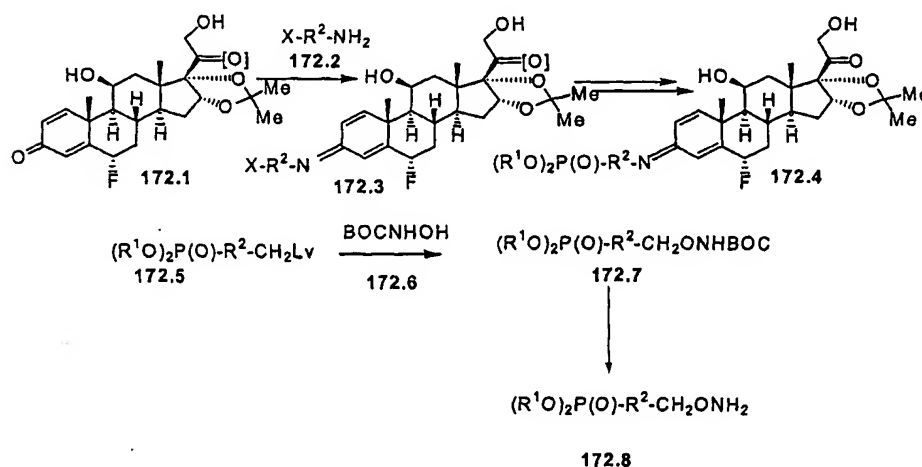
The 21-hydroxyl group is protected, for example, by conversion to the acetate ester, by reaction with one molar equivalent of acetyl chloride in

dichloromethane/pyridine. The 21-acetoxy group is removed by reaction with one molar equivalent of lithium hydroxide in aqueous dimethoxyethane.

Alternatively, the 21-hydroxyl group is protected by conversion to the tert. butyl dimethylsilyl ether, by reaction in dimethylformamide solution with one molar equivalent of tert. butylchlorodimethylsilane and imidazole, as
 5 described in *J. Am. Chem. Soc.* 94:6190 (1972). The silyl ether is removed by reaction with tetrabutylammonium fluoride in tetrahydrofuran solution, as described in *J. Am. Chem. Soc.* 94:6190 (1972).

The protected compound 171.2 is then converted into the phosphonate-containing analog 171.3 and the protecting group or groups are then removed, as
 10 described above, to give the phosphonate 171.4.

Example 172 Preparation of Representative Flunisolid Derivatives

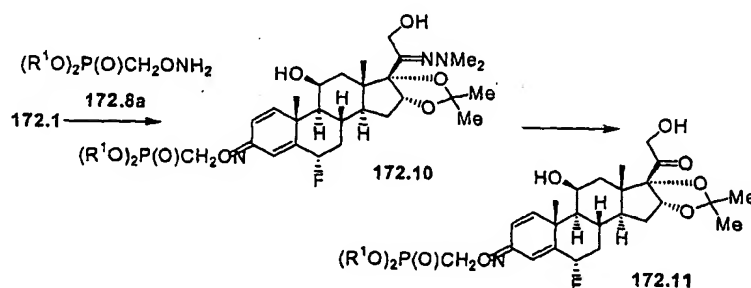


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The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the ketone-protected derivative 172.1 is reacted with
 20 an amine or hydroxylamine 172.2, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is

subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime 172.3. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.* 86:133 (1978) and in *J. Mass. Spectrom.* 30:497 (1995). The protecting group is then removed to afford the 20-keto phosphonate product 172.4.

The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated above. In this procedure, a phosphonate 172.5, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine 172.6 (Aldrich) to produce the ether 172.7. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether 172.8. The above procedure is also employed for the preparation of substituted hydroxylamines which are precursors to phosphonates.

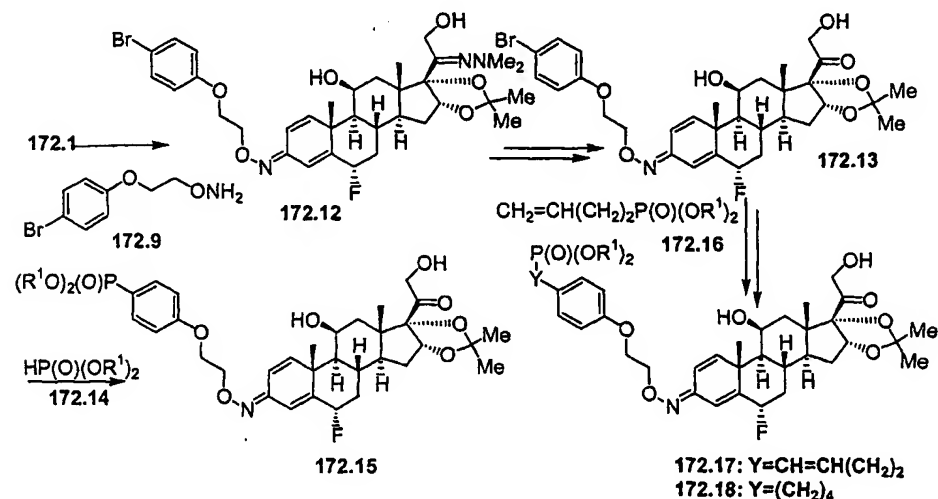


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The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate 172.1, in which the 20-ketone is protected as the dimethyl hydrazone derivative, is reacted with a dialkyl phosphonomethyl hydroxylamine 172.8a, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tetrahedron Lett.* 27:1477 (1986)) and BOC-hydroxylamine, to afford the

oxime **172.10**. Deprotection affords the 20-keto phosphonate **172.11**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

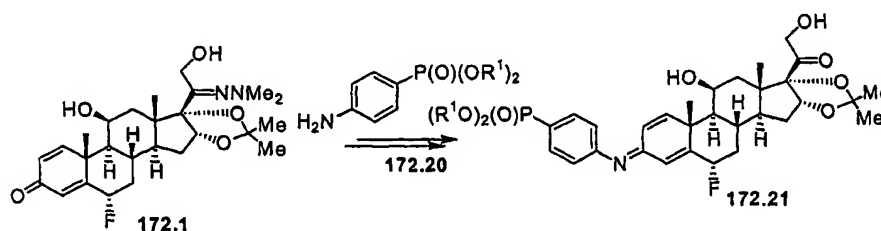
Using the above procedures, but employing, in place of the hydroxylamine ether **172.8a**, different oxime ethers **172.2**, the corresponding products **172.4** are obtained.



The preparation of compounds in which the phosphonate group is attached by means of a phenoxyethoxy oxime group is illustrated above. In this procedure, the dienone **172.1**, in which the 20-ketone is protected as the dimethyl hydrazone, is reacted, as described above, with O-(4-bromophenoxy)ethyl hydroxylamine **172.9**, prepared as described above from 4-bromophenoxyethyl bromide (FR 1481052), and BOC-protected hydroxylamine **172.6**, to give the oxime **172.12**. The protecting group is then removed to yield the 20-keto product **172.13**. The latter product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **172.14** to afford the phosphonate **172.15**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.* 35:1371 (1992). The reaction is performed at ca. 100°C in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Alternatively, the bromo compound 172.13 is coupled with a dialkyl butenyl phosphonate 172.16 (*Org. Lett.* 3:217 (2001)) to afford the phosphonate 172.17. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry* 503ff (Plenum, 2001) and in *Acc. Chem. Res.* 12:146 (1979). The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxane, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product 172.17 is reduced, for example by reaction with diimide, to produce the saturated analog 172.18. The reduction of olefinic bonds is described in R. C. Larock, *Comprehensive Organic Transformations* 6ff (VCH 1989). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

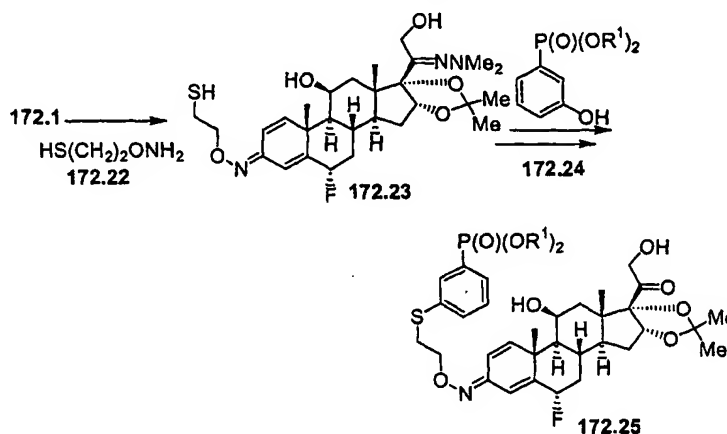
Using the above procedures, but employing, in place of the bromophenoxyethyl reagent 172.9, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, products analogous to the compounds 172.15, 172.17 and 172.18 are obtained.



The preparation of phosphonates in which the phosphonate is attached by means of a 4-phenylimino group is illustrated above. In this procedure, the substrate 172.1, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with a dialkyl 4-aminophenyl phosphonate 172.20 (Epsilon), to give, after deprotection, the imine product 172.21. The imine forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an

acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions.

Using the above procedures, but employing, in place of the 4-aminophenyl phosphonate 172.20 different amino-substituted aryl or heteroaryl phosphonates, products analogous to 172.21 are obtained.



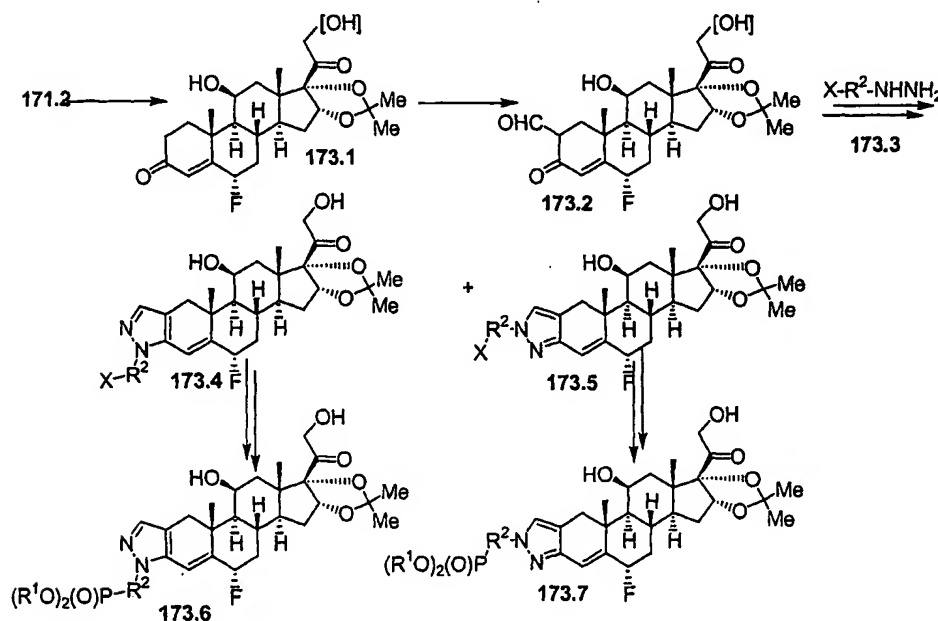
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The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and a thioether linkage is illustrated above. In this procedure, the dienone 172.1, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with 2-mercaptoethyl hydroxylamine 172.22 (10 *Bioorganicheskaya Khim.* 12:1662 (1986)) to yield the oxime 172.23. The reaction of steroidal 1,4-dien-3-ones with hydroxylamines is described in *J. Steroid Bioch.* 7:795 (1976). The reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product 172.23 (15 is then coupled, in a Mitsunobu reaction, with a dialkyl 3-hydroxyphenyl phosphonate 172.24 (Aurora), to yield, after deprotection, the thioether oxime 172.25. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in R. C. Larock, *Comprehensive Organic Transformations* 448 (VCH, 1989), in F.A. Carey and R. J. Sundberg, *Advanced Organic Chemistry, Part B* 153-4 (Plenum, 2001), and in *Org. React.* 42:335, (20 (1992). The phenol and the hydroxyl or mercapto component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.* 42:335-656

(1992).

Using the above procedures, but employing, in place of the mercapto-substituted hydroxylamine 172.24, different mercapto-substituted hydroxylamines, and/or different hydroxyaryl phosphonates, the products analogous to 172.25 are obtained.

Example 173 Preparation of Representative Flunisolide Derivatives



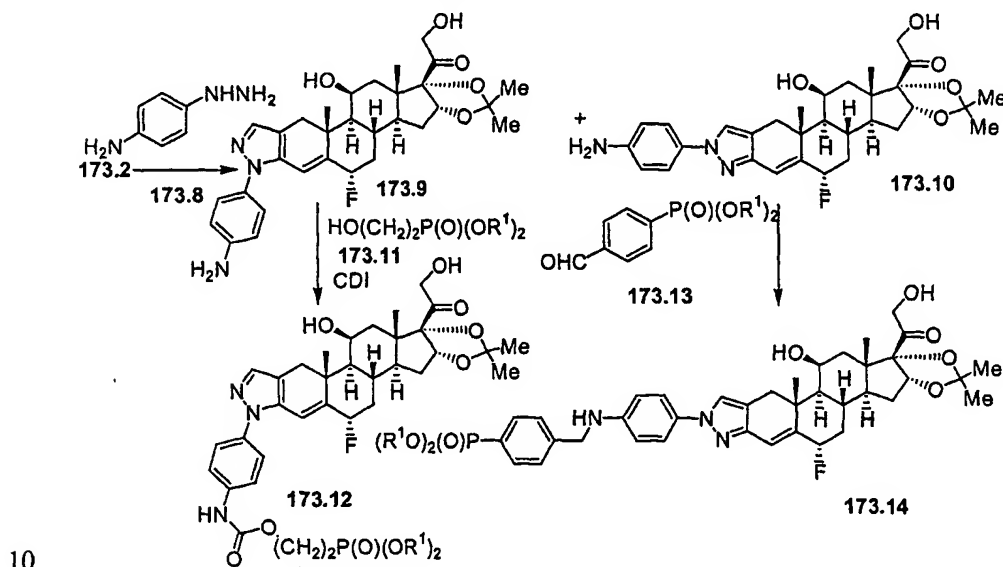
10

The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and/or a variable carbon chain is illustrated above. In this procedure, the dienone 171.2, in which the 21-hydroxyl group is protected is reduced to afford the 1,2-dihydro product 173.1. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.* 44:602 (2001). The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.* 86:1520 (1964), to afford the 2-formyl product 173.2. This compound is then reacted with an alkyl,

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aralkyl, aryl or heteroaryl hydrazine 173.3, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields, after
 5 deprotection of the 21-hydroxyl group, the isomeric 2'- and 1'-aryl pyrazoles 173.4 and 173.5. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.* 86:1520 (1964). The pyrazoles 173.4 and 173.5 are then transformed into the phosphonates 173.6 and 173.7.

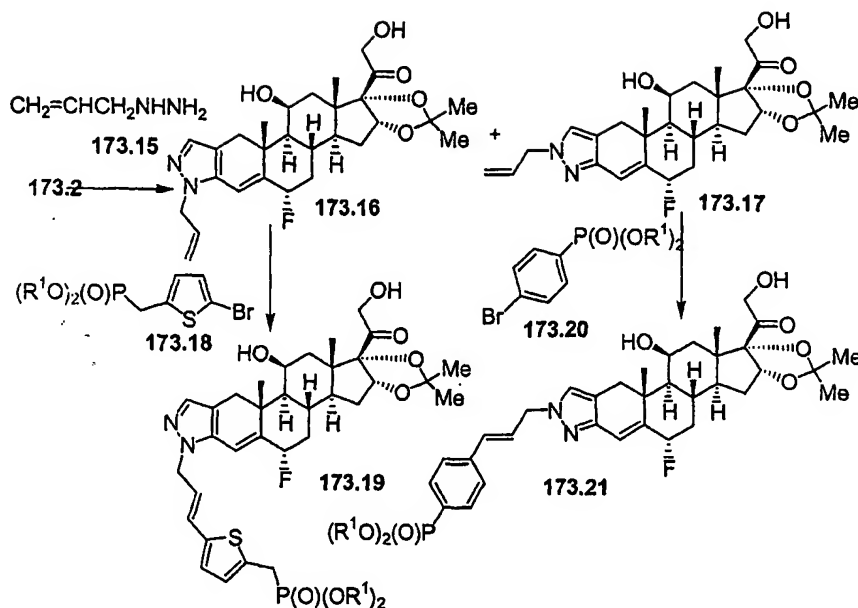


The preparation of phosphonates in which the phosphonate is attached by means of a carbamate or an amine linkage is illustrated above. In this procedure, the ketoaldehyde 173.2 is reacted, as described above, with 4-aminophenyl
 15 hydrazine 173.8 (*Syn. Comm.* 4:57 (1974)) to give the pyrazoles 173.9 and 173.10. The 2'-substituted isomer 173.9 is then reacted in dichloromethane solution with one molar equivalent of a dialkyl 2-hydroxyethyl phosphonate 173.11 (Aldrich) and carbonyl diimidazole (CDI) to give the carbamate 173.12. The preparation of carbamates is described in Comprehensive Organic
 20 Functional Group Transformations Vol. 6 416ff (A. R. Katritzky, ed., Pergamon, 1995) and in S.R.Sandler and W. Karo, Organic Functional Group Preparations 260ff (Academic Press, 1986). In the procedure, the amine is reacted in an inert

aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate.

The isomeric pyrazole 173.10 is reacted in a reductive amination procedure, in tetrahydrofuran solution at ambient temperature, with one molar equivalent of a dialkyl 4-formylphenyl phosphonate 173.13 (Epsilon) and sodium cyanoborohydride to yield the amine phosphonate 173.14. The preparation of amines by means of reductive amination procedures is described, for example, in R. C. Larock, Comprehensive Organic Transformations, 421 (VCH) and in F.A. Carey and R. J. Sundberg, Advanced Organic Chemistry, Part B 269 (Plenum, 2001). In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in *J. Org. Chem.* 55:2552 (1990).

Using the above procedures, but employing different amino-substituted hydrazines, and/or different hydroxy- or formyl-substituted phosphonates, the products analogous to 173.12 and 173.14 are obtained.



The preparation of the phosphonates in which the phosphonate group is attached by means of a propenyl group and an aromatic ring is illustrated above.

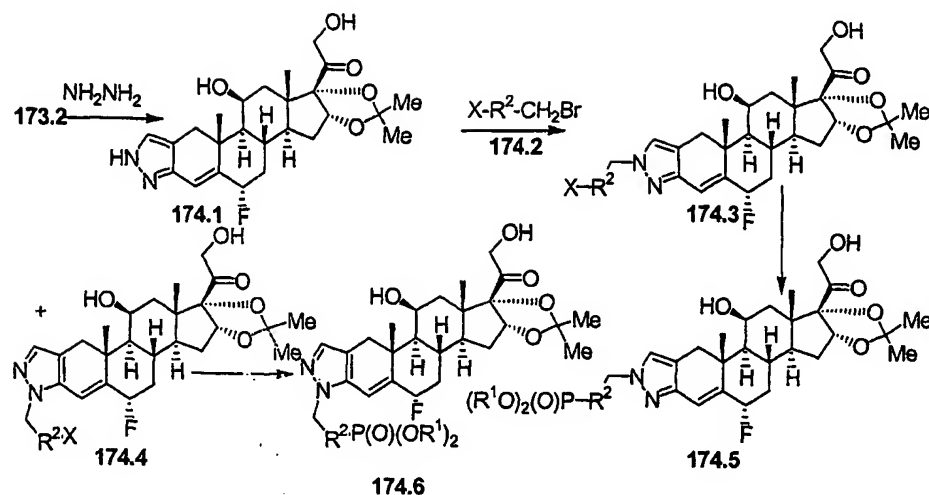
5 In this procedure, the ketoaldehyde **173.2** is reacted, as described above, with allyl hydrazine **173.15** (*Zh. Org. Khim.* 3:983 (1967)) to produce the pyrazoles **173.16** and **173.17**. The 2'-substituted isomer **173.16** is then coupled by means of a Heck reaction, as described above, with a dialkyl 5-bromo-2-thienylmethyl phosphonate **173.18** (*Syn.* 455 (2003)) to give the phosphonate **173.19**.

10 Alternatively, the 1'-substituted pyrazole **173.22** is coupled in a Heck reaction, as described above, with a dialkyl 4-bromophenyl phosphonate **173.20** (*J. Organomet. Chem.* 581:62 (1999)) to prepare the phenylpropenyl phosphonate **173.21**.

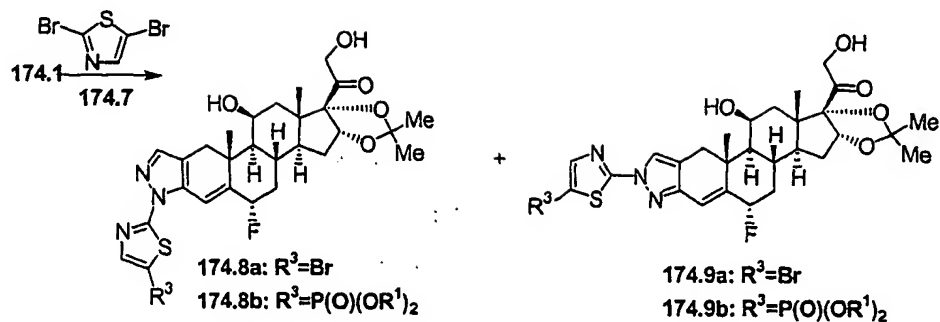
15 Using the above procedures, but employing, in place of the allyl hydrazine **173.15**, different alkenyl hydrazines, and/or different dialkyl bromo-substituted phosphonates, the products analogous to the compounds **173.19** and **173.21** are obtained.

Example 174 Preparation of Representative Flunisolide Derivatives

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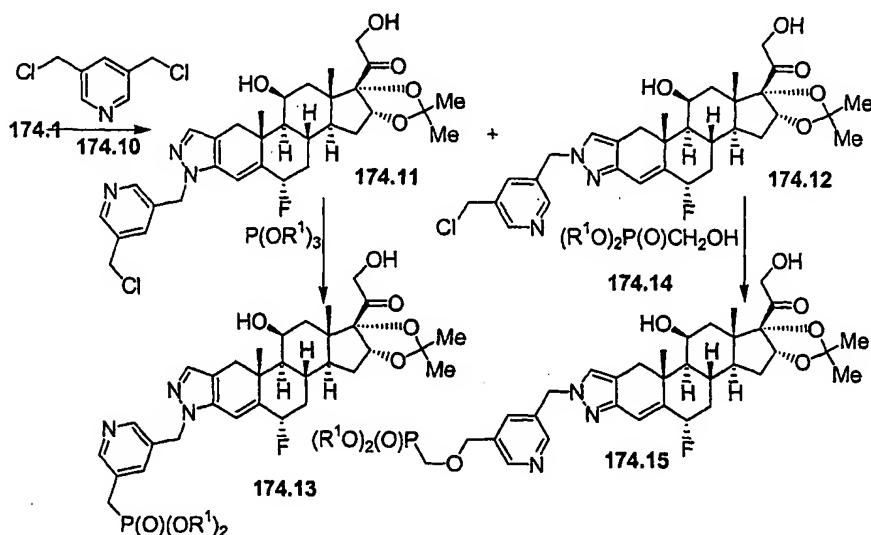


The preparation of phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde 173.2 is reacted with hydrazine to afford the pyrazole derivative 174.1. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.* 86:1520 (1964). The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound 174.2, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products 174.3 and 174.4. The alkylation of substituted pyrazoles is described, for example, in T. L. Gilchrist, *Heterocyclic Chemistry* 309 (Longman, 1992). The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products 174.3 and 174.4 are, except in cases where X is dialkylphosphono, converted into the phosphonates 174.5 and 174.6, using the procedures described herein.



Representative compounds of the invention can be prepared as illustrated above. The pyrazole 174.1 is reacted in dimethylformamide solution at 70°C with one molar equivalent of 2,5-dibromothiazole 174.7 (Aldrich) and lithium hexamethyl disilazide, to give the pyrazoles 174.8a and 174.9a. The products are then coupled, as described above, with a dialkyl phosphite to yield the phosphonates 174.8b and 174.9b.

Using the above procedures, but employing different dibromo-substituted heterocycles, the products analogous to 174.8b and 174.9b are obtained.



Representative compounds of the invention can be prepared as illustrated above. The pyrazole 174.1 is reacted in tetrahydrofuran solution with one molar equivalent of 3,5-bis(chloromethyl)pyridine 174.10 (*Eur. J. Inorg. Chem.* 2:163 (1998)) and potassium hexamethyl disilazide, to give the alkylation products

174.11 and 174.12. The 2'-substituted isomer 174.11 is then reacted, in an Arbuzov reaction, with a trialkyl phosphite and a catalytic amount of potassium bromide, to yield the phosphonate 174.13. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.* 115 (1992). In this procedure, in which a
5 halo substituent is converted into the corresponding phosphonate, the substrate is heated at from about 60°C to about 160°C with a five to fifty-fold molar excess of a trialkyl phosphite, to effect the transformation.

The 2'-substituted pyrazole 174.12 is reacted at 70°C in dimethylformamide solution with one molar equivalent of a dialkyl
10 hydroxymethyl phosphonate 174.14 (Aldrich) and cesium carbonate, to give the ether phosphonate 174.15.

Using the above procedures, but employing different dihalides, and/or different hydroxyl-substituted phosphonates, products analogous to 174.13 and 174.15 are obtained.

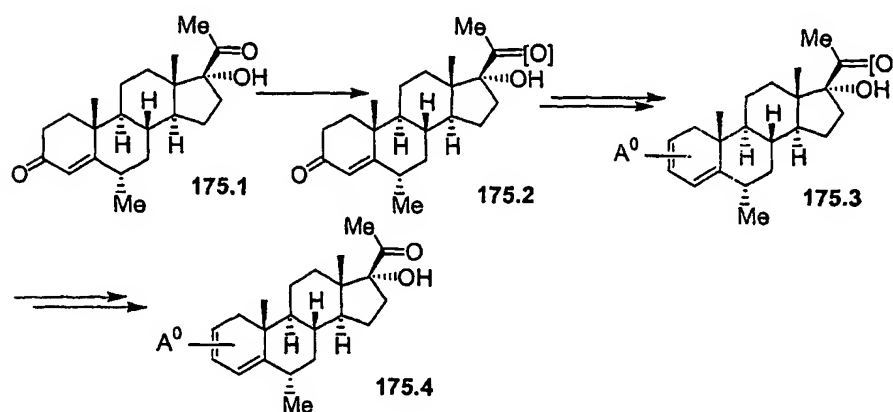
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Examples 175-178 Medroxyprogesterone Derivatives

20 The synthesis of representative phosphonate derivatives of medroxyprogesterone is outlined in Examples 175-178. In these Examples, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art.

25 Protection and deprotection of functional groups are described, for example, in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The protection and deprotection of steroidal ketones and alcohols is described in *Organic Reactions in Steroid Chemistry*, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff.

30 Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], etc.

Example 175 Preparation of Representative Medroxyprogesterone

Representative compounds of the invention can be prepared as illustrated above. The 20-ketone group of medroxyprogesterone **175.1** (US Patent Nos. 3043832, 3061616, and 3377364) is protected to afford the derivative **175.2**. The ketone is protected, for example, by conversion to the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, 77:1904 (1955). Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in *J. Chem. Soc. Chem. Comm.* 1351 (1987).

Alternatively, the 20-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone **175.1** with N,N-dimethylhydrazine in ethanol-acetic acid, as described in *Org. Syn.* 50:102 (1970). The group is removed by treatment with sodium acetate and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.* 101:5841 (1979).

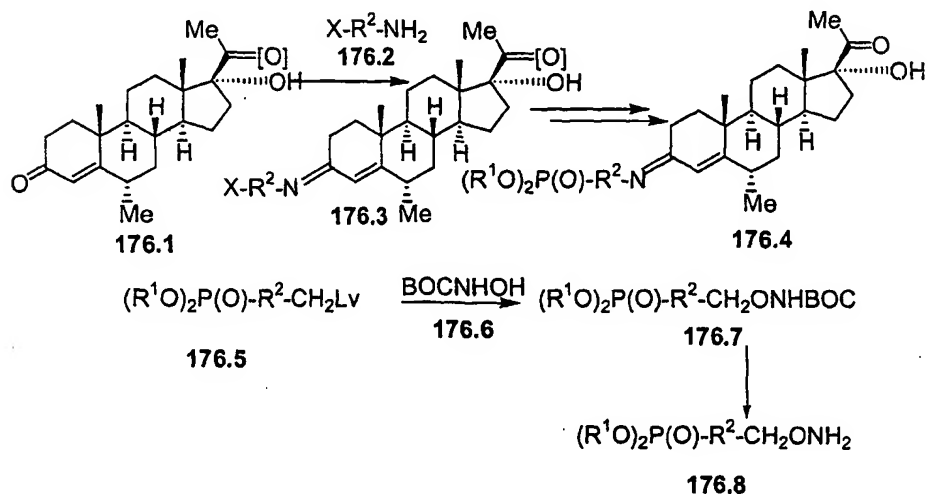
Alternatively, the 20-ketone is protected as the diethylamine adduct. In this procedure, the substrate **175.1** is reacted with titanium tetrakis(diethylamide), as described in *J. Chem. Soc. Chem. Comm.* 406 (1983), to afford the adduct. The ketone is deprotected by reaction with water in an aqueous organic solvent.

The protected compound **175.2** is then converted into the phosphonate-containing analog **175.3**, using the procedures described below, and the

protecting group or groups are then removed, as described above, to give the phosphonate 175.4.

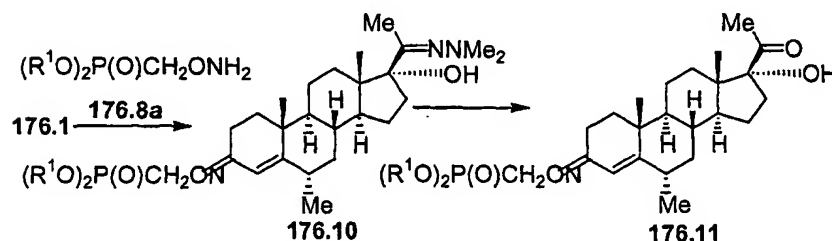
Example 176 Preparation of Representative Medroxyprogesterone

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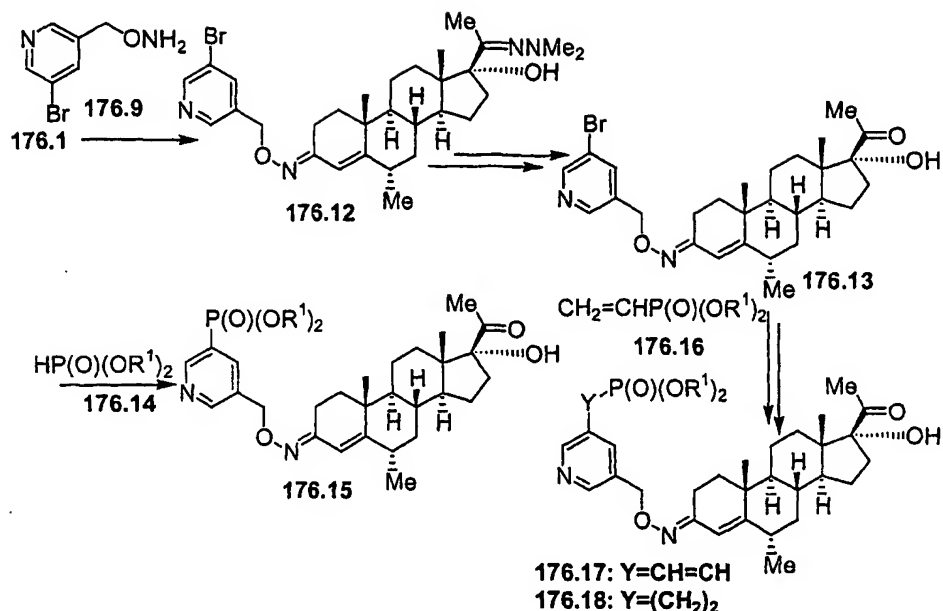
The preparation of phosphonates in which the phosphonate is attached by means of an imine or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the ketone-protected derivative **176.1** is reacted with a hydroxylamine or amine **176.2**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the oxime **176.3**. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.* 86:133 (1978) and in *J. Mass. Spectrom.* 30:497 (1995). The protecting group is then removed to afford the 20-keto phosphonate product **176.4**.

The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated. In this procedure, a phosphonate **176.5**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine **176.6** (Aldrich) to produce the ether **176.7**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether **176.8**. The above procedure is also employed for the preparation of substituted hydroxylamines which are precursors to phosphonates.



The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate **176.1**, in which the 20-ketone is protected as the dimethyl hydrazone derivative, is reacted with a dialkyl phosphonomethyl hydroxylamine **176.8a**, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tetrahedron Lett.* 27:1477 (1986)) and BOC-hydroxylamine, to afford the oxime **176.10**. Deprotection affords the 20-keto phosphonate **176.11**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether **176.8a**, different oxime ethers **176.2**, the corresponding products **176.4** are obtained.

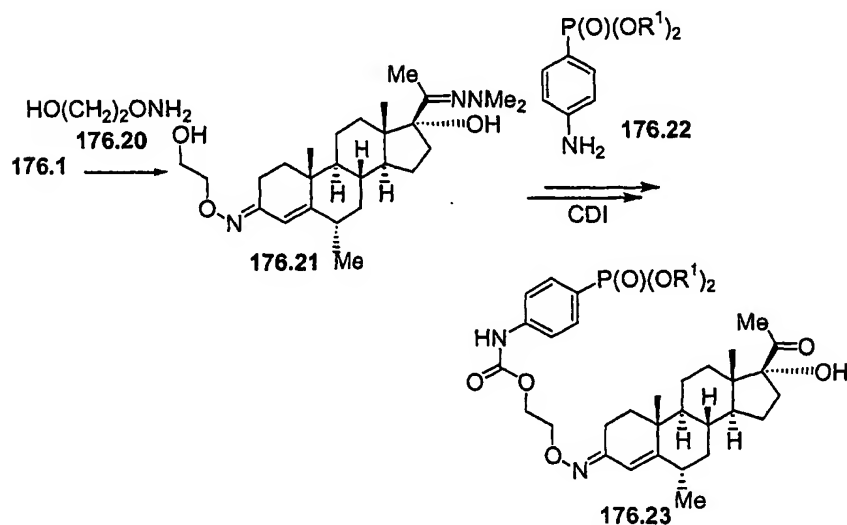


The preparation of compounds in which the phosphonate group is attached by means of a pyridylmethoxy oxime group is illustrated above. In this procedure, the enone **176.1**, in which the 20-ketone is protected as the dimethyl hydrazone, is reacted, as described above, with O-(5-bromo-3-pyridylmethoxy)hydroxylamine **176.9**, prepared as described above from 5-bromo-3-bromomethylpyridine (WO 9528400) and BOC-protected hydroxylamine **176.6**, to give the oxime **176.12**. The protecting group is then removed to yield the 20-keto product **176.13**. The latter product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **176.14** to afford the phosphonate **176.15**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.* 35:1371 (1992). The reaction is performed at ca. 100°C in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Alternatively, the bromo compound **176.13** is coupled with a dialkyl vinylphosphonate **176.16** (Aldrich) to afford the phosphonate **176.17**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry* 503ff (Plenum, 2001) and in *Acc. Chem. Res.* 12:146 (1979). The aryl bromide

and the olefin are coupled in a polar solvent such as dimethylformamide or dioxane, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product 176.17 is reduced, for example by reaction with diimide, to produce the saturated analog 176.18. The reduction of olefinic bonds is described in R. C. Larock, Comprehensive Organic Transformations 6ff (VCH 1989). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromopyridyl reagent 176.9, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, products analogous to the compounds 176.15, 176.17 and 176.18 are obtained.



The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and a carbamate linkage is illustrated above. In this procedure, the enone 176.1, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with 2-hydroxyethyl hydroxylamine 176.20 (*J. Chem. Soc. Chem. Comm.* 903 (1986)) to yield the oxime 176.21. The reaction

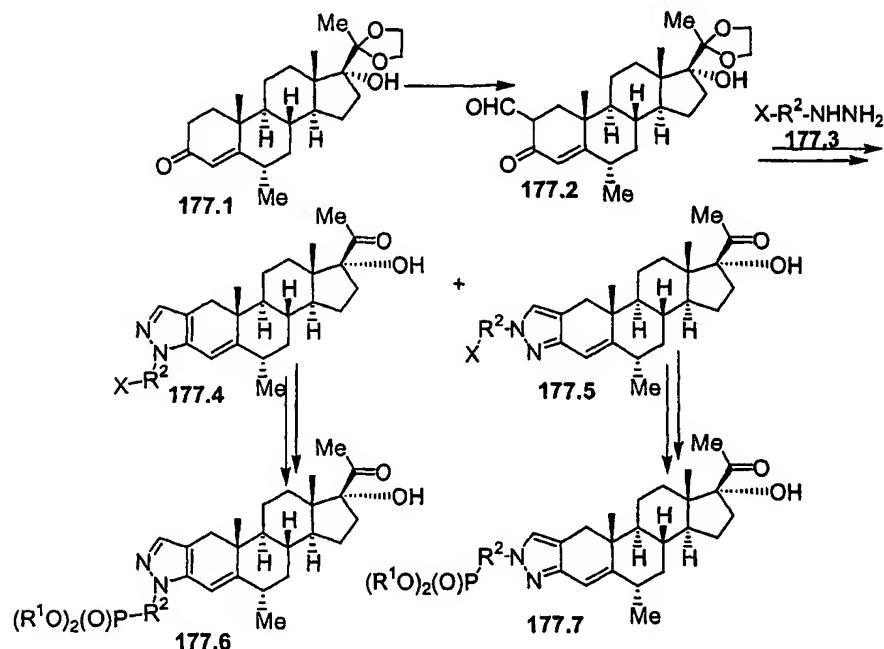
of unsaturated steroidal ketones with hydroxylamines is described in *J. Steroid Bioch.* 7:795 (1976). The reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product 176.21 is then

5 coupled with a dialkyl 4-aminophenyl phosphonate 176.22 (Epsilon) and carbonyl diimidazole, to yield, after deprotection, the carbamate oxime 176.23. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations Vol. 6 416ff (A. R. Katritzky, ed., Pergamon, 1995) and in S. R. Sandler and W. Karo, Organic Functional Group Preparations

10 260ff (Academic Press, 1986). In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the

15 carbamate.

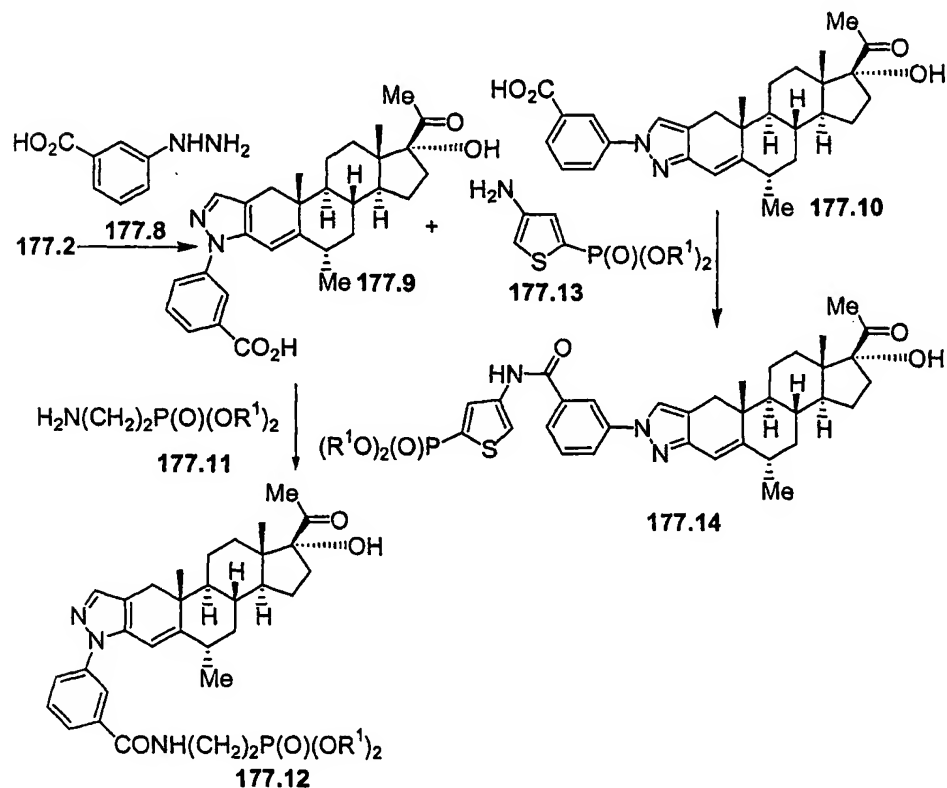
Using the above procedures, but employing, in place of the hydroxy-substituted hydroxylamine 176.20, different hydroxy-substituted hydroxylamines, and/or different amino-substituted phosphonates, the products analogous to 176.23 are obtained.

Example 177 Preparation of Representative Medroxyprogesterone

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The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and/or a variable carbon chain is illustrated above. In this procedure, the enone 177.1 in which the 20-ketone is protected as the cyclic ethylene ketal, is reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.* 86:1520 (1964), to afford the 2-formyl product 177.2. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine 177.3, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields, after deprotection of the 20-ketone, the isomeric 2'- and 1'-aryl pyrazoles 177.4 and 177.5. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am.*

Chem. Soc. 86:1520 (1964). The pyrazoles 177.4 and 177.5 are then transformed into the phosphonates 177.6 and 177.7.



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The preparation of phosphonates in which the phosphonate is attached by means of a phenyl ring and an amide linkage is illustrated above. In this procedure, the ketoaldehyde 177.2 is reacted, as described above, with 3-carboxyphenyl hydrazine 177.8 (Apin) to give the pyrazoles 177.9 and 177.10.

- 10 The 2'-substituted isomer 177.9 is then reacted in dimethylformamide solution at ambient temperature with one molar equivalent of a dialkyl 2-aminoethyl phosphonate 177.11 (Aldrich) and dicyclohexyl carbodiimide, to give the amide phosphonate 177.12. The preparation of amides from carboxylic acids and derivatives is described, for example, in S.R. Sandler and W. Karo, *Organic*
- 15 *Functional Group Preparations* 274 (Academic Press, 1968) and R. C. Larock, *Comprehensive Organic Transformations* 972ff (VCH, 1989). The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for

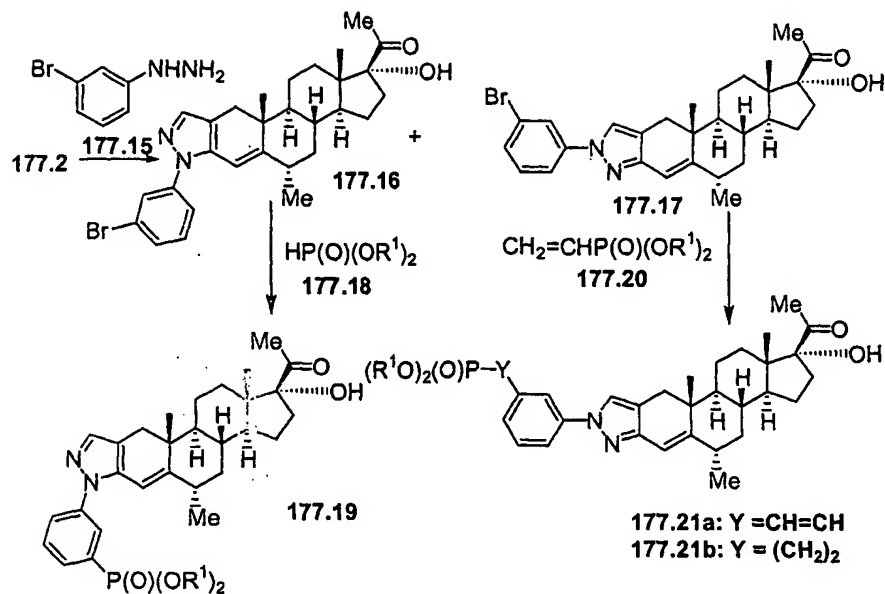
example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

5 Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolidine and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

10 The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

15 The isomeric pyrazole 177.10 is reacted, as described above, with one molar equivalent of a dialkyl 4-amino-2-thienyl phosphonate R2.20, prepared by the palladium catalyzed coupling reaction, as described above, between 4-amino-2-bromothiophene (*Tetrahedron Lett.* 43:3295 (1987)) and a dialkyl phosphite, to give the amide phosphonate 177.14.

20 Using the above procedures, but employing different carboxy-substituted hydrazines, and/or different amino-substituted phosphonates, the products analogous to 177.12 and 177.14 are obtained.

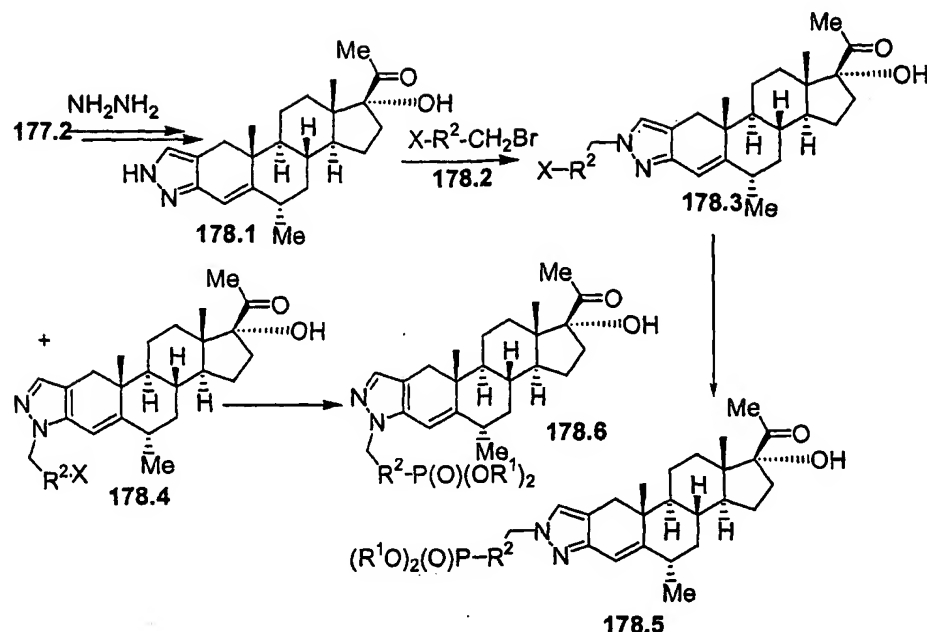


The preparation of the phosphonates in which the phosphonate group is attached by means of a phenyl group or a phenyl group and a carbon chain is illustrated above. In this procedure, the ketoaldehyde 177.2 is reacted, as described above, with 3-bromophenyl hydrazine 177.15 (Fluka) to produce the pyrazoles 177.16 and 177.17. The 2'-substituted isomer 177.16 is then coupled, as described above, with a dialkyl phosphite 177.18 to afford the phosphonate 177.19.

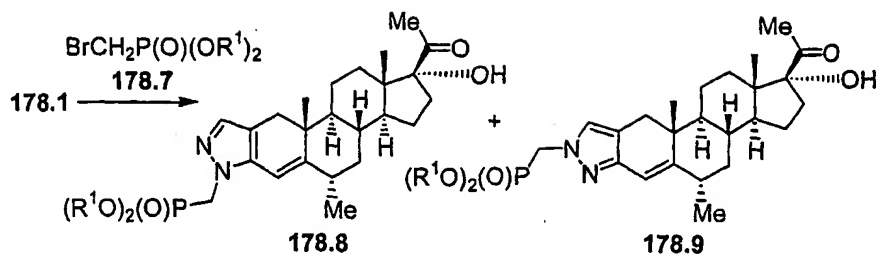
Alternatively, the 1'-substituted pyrazole 177.17 is coupled, as described above, with a dialkyl vinylphosphonate 177.20 (Aldrich) and a palladium catalyst to prepare the vinyl phosphonate 177.21a. Optionally, the product is reduced, as described above, to give the analog 177.21b.

Using the above procedures, but employing, in place of the bromophenyl hydrazine 177.15, different bromo-substituted hydrazines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds 177.19 and 177.21 are obtained.

Example 178 Preparation of Representative Medroxyprogesterone



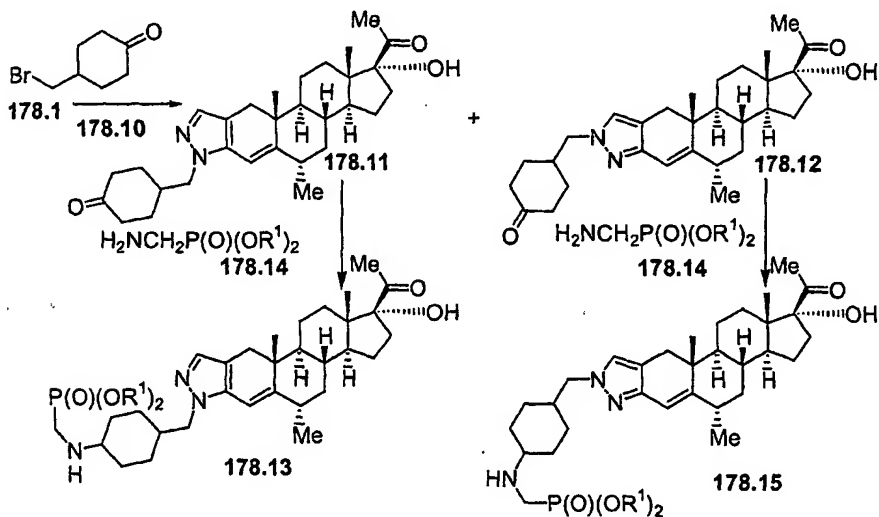
- The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde 177.2 is reacted with hydrazine to afford, after deprotection of the 20-ketone, the pyrazole derivative 178.1. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.* 86:1520 (1964). The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound 178.2, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products 178.3 and 178.4. The alkylation of substituted pyrazoles is described, for example, in T. L. Gilchrist, *Heterocyclic Chemistry* 309 (Longman, 1992). The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products 178.3 and 178.4 are, except in cases where X is dialkylphosphono, converted into the phosphonates 178.5 and 178.6, using the procedures described herein.



Representative compounds of the invention can be prepared as illustrated above. The pyrazole **178.1** is reacted in dimethylformamide solution at 70°C with one molar equivalent of a dialkyl 4-bromomethyl phosphonate **178.7** (Lancaster) and lithium hexamethyl disilazide, to give the pyrazoles **178.8** and **178.9**.

Using the above procedures, but employing different bromo-substituted phosphonates, the products analogous to **178.8** and **178.9** are obtained.

10



Representative compounds of the invention can be prepared as illustrated above. The pyrazole **178.1** is reacted in tetrahydrofuran solution with 4-bromomethyl cyclohexanone **178.10** (WO 9737959) and potassium hexamethyl disilazide, to give the alkylation products **178.11** and **178.12**. The 2'-substituted isomer **178.11** is then reacted, in a reductive amination reaction, with a dialkyl aminomethyl phosphonate **178.14** (Interchim) and sodium triacetox

borohydride, to yield the amine phosphonate 178.13. The preparation of amines by means of reductive amination procedures is described, for example, in R. C. Larock, Comprehensive Organic Transformations 421 (VCH) and in F.A. Carey and R. J. Sundberg, Advanced Organic Chemistry, Part B 269 (Plenum, 2001).

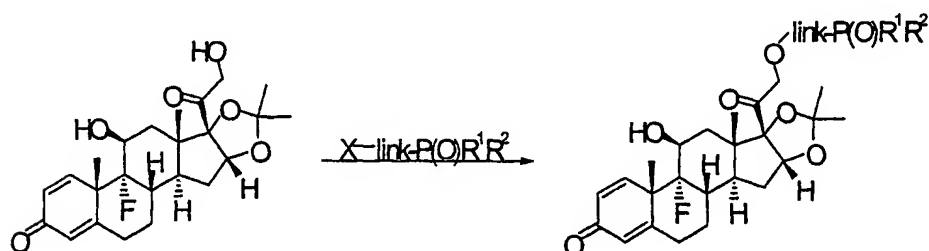
5 In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in *J. Org. Chem.* 55:2552 (1990).

10 The 1'-substituted pyrazole 178.12 is converted by the same reaction into the isomeric amine phosphonate 178.15.

Using the above procedures, but employing different bromo-substituted aldehydes and ketones, and/or different amino-substituted phosphonates, products analogous to 178.13 and 178.15 are obtained.

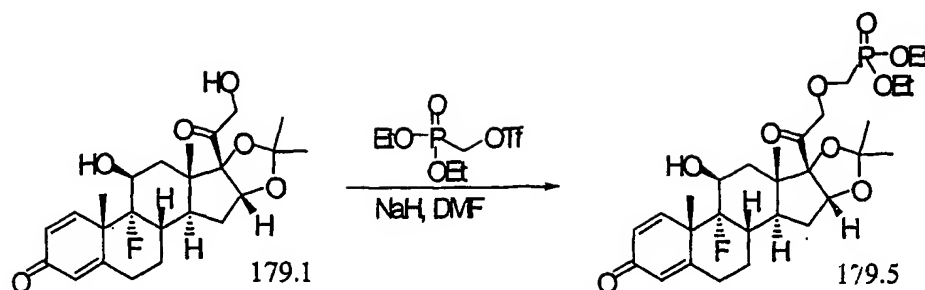
15

Example 179 Preparation of Representative Compounds of the Invention



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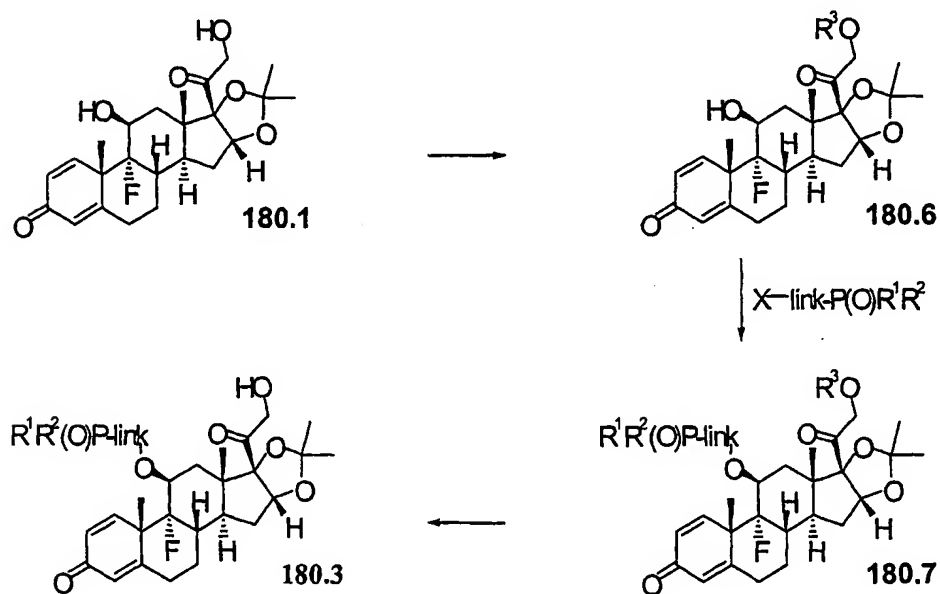
As illustrated above, derivatives of the C-21 primary hydroxy group are readily prepared by alkylating triamcinolone acetonide with the appropriate phosphonate. A specific compound of the invention can be prepared as follows.



- 5 After chemoselective extraction of the primary hydroxy proton in **179.1** using one equivalent of sodium hydride, the phosphonate triflate is added to provide the ether **179.5**.

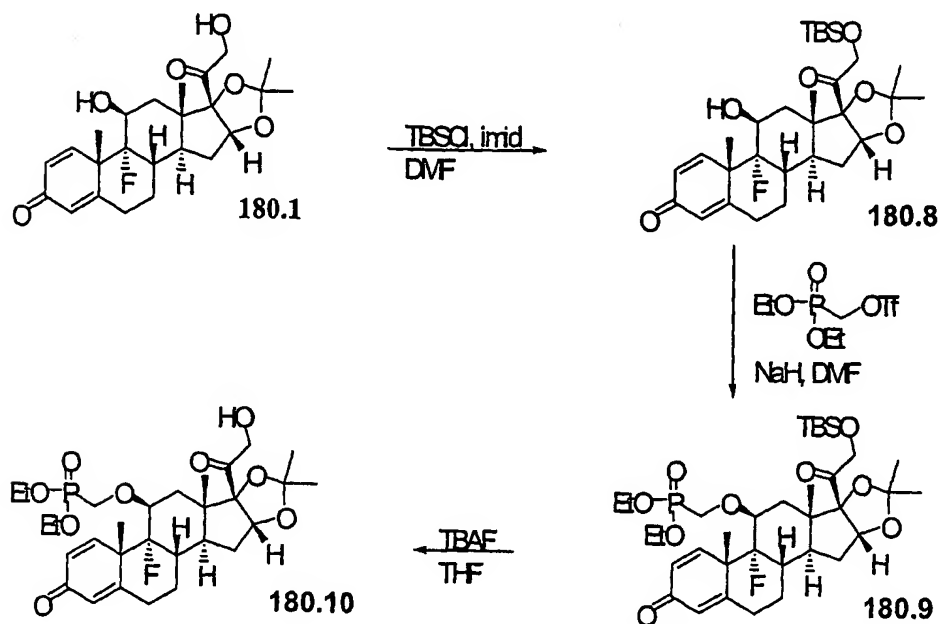
Example 180 Preparation of Representative Compounds of the Invention

10



- As illustrated above, by taking advantage of the reactivity difference
- 15 between the primary and secondary hydroxy groups, the primary hydroxy group is masked by an appropriate protecting group. After alkylation at the secondary

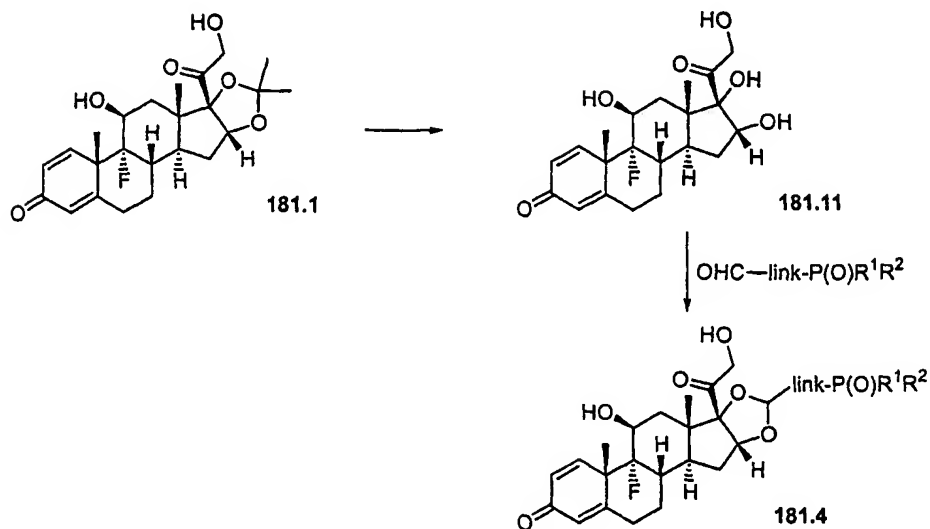
hydroxy moiety of **180.6** with a leaving group-attached phosphonate and subsequent deprotection, desired analog **180.3** is obtained. A specific compound of the invention can be prepared as follows.



5

Triamcinolone acetonide **180.1** is chemoselectively protected as its silyl ether using the standard TBSCl and imidazole conditions. (*J. Am. Chem. Soc.* 1972, 94, 6190) Alkylation at the exposed secondary hydroxy group with sodium hydride and the phosphonate triflate furnishes the intermediate **180.9**. Final TBAF deprotection of the silyl ether affords the desired product **180.10**.

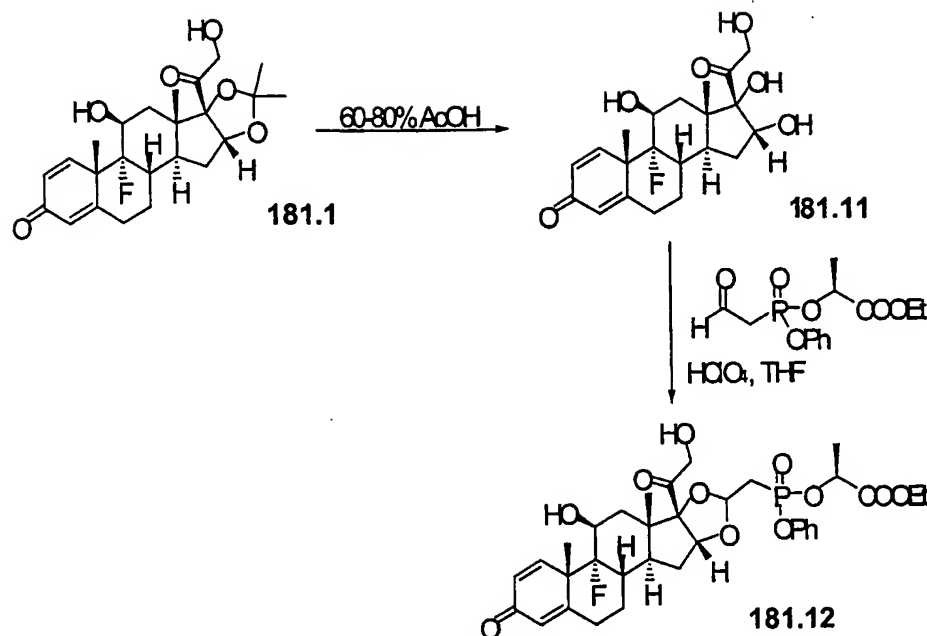
10

Example 181 Preparation of Representative Compounds of the Invention

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Representative compounds of the invention can be prepared as illustrated above. Phosphonate derivatives of the acetal are readily prepared from acidic hydrolysis of triamcinolone acetonide **181.1** to the diol **181.11**. Acetylation of the diol with a phosphonate aldehyde furnishes the desired acetal **181.4**. A

10 specific compound of the invention can be prepared as illustrated below.



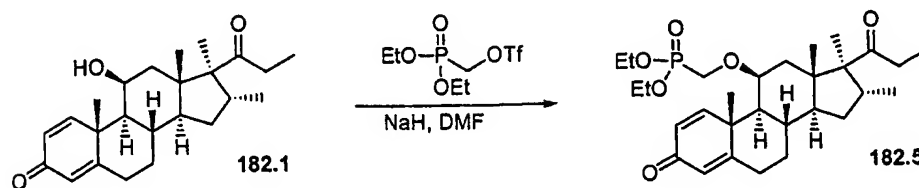
- 5 Triamcinolone acetonide **181.1** is first hydrolyzed in aqueous acetic acid. (*Can. J. Chem.* **1983**, *61*, 634). The resulting diol **181.11** is acetalized with the phosphonate aldehyde and perchloric acid, affording the acetal **181.12**. (*J. Med. Chem.* **1996**, *39*, 4888-4896)

10 **Example 182 Preparation of Representative Compounds of the Invention**



- 15 Representative compounds of the invention can be prepared as illustrated above. Derivatization at the C-11 hydroxy group is accomplished through alkylation of rimexolone **182.1** with the appropriate phosphonate, furnishing analogs of

formula **182.2**. A specific compound of the invention can be prepared as illustrated below.

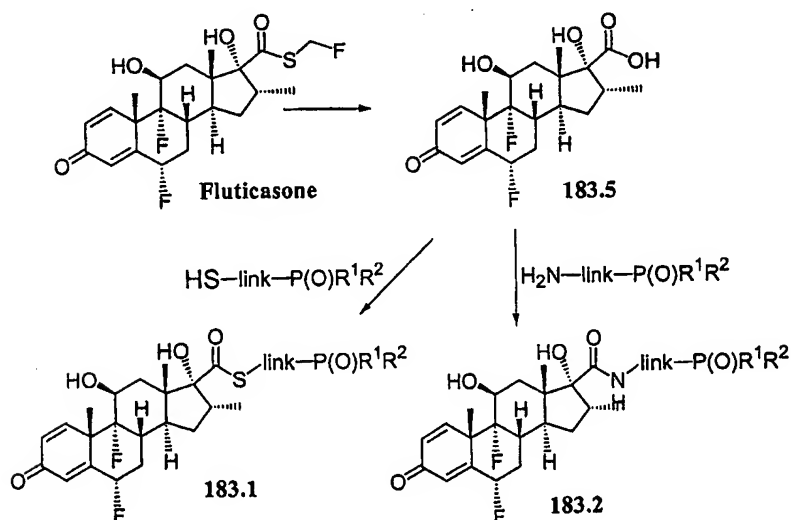


5

After sodium hydride extraction of the hydroxy proton in **182.1**, diethyl phosphonate triflate is added to afford ether **182.5**.

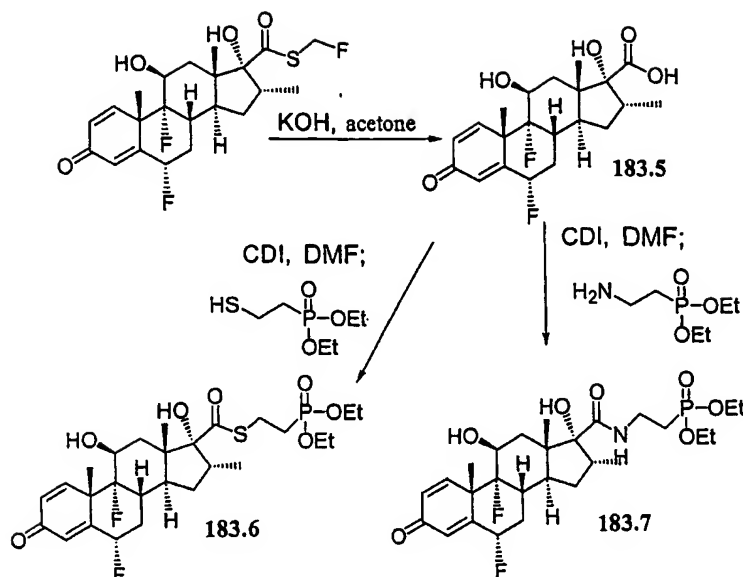
Example 183 Preparation of Representative Compounds of the Invention

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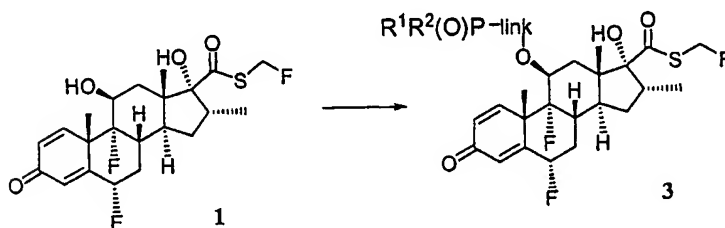
15

Representative compounds of the invention can be prepared as illustrated above. Derivatives of the carbonyl at C-17 are readily prepared from saponification of fluticasone to the carboxylic acid **183.5**. Activation of the carboxylic acid, followed by reaction with thiophosphonate or aminophosphonate nucleophile furnishes the desired thioester **183.1** and amide **183.2**, respectively. Specific compounds of the invention can be prepared as follows.



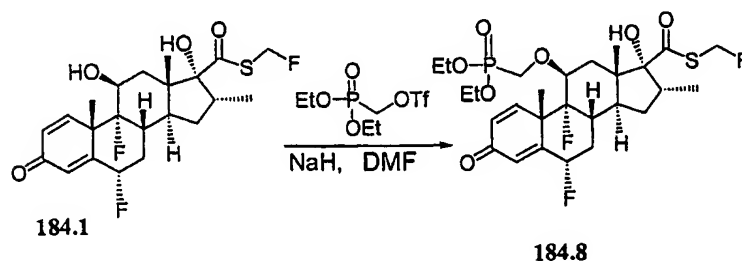
Fluticasone is first saponified with potassium hydroxide in acetone. (*Synthesis* 2002, 921-927) The resulting carboxylic acid **183.5** is activated to the carboxylic acid imidazole by the addition of 1,1'-carbonyldiimidazole (CDI). (*J. Med. Chem.* 1994, 37, 3717-3729) Treatment with the thiophosphonate affords thioester **183.6**. Magnesium ethoxide may be added to help enhance the reactivity. (*Tetrahedron Lett.* 1981, 22, 3245-3246) Alternatively, the carboimidazole intermediate derived from **183.5** can be reacted with the aminophosphonate to produce amide **183.7**.

Example 184 Preparation of Representative Compounds of the Invention



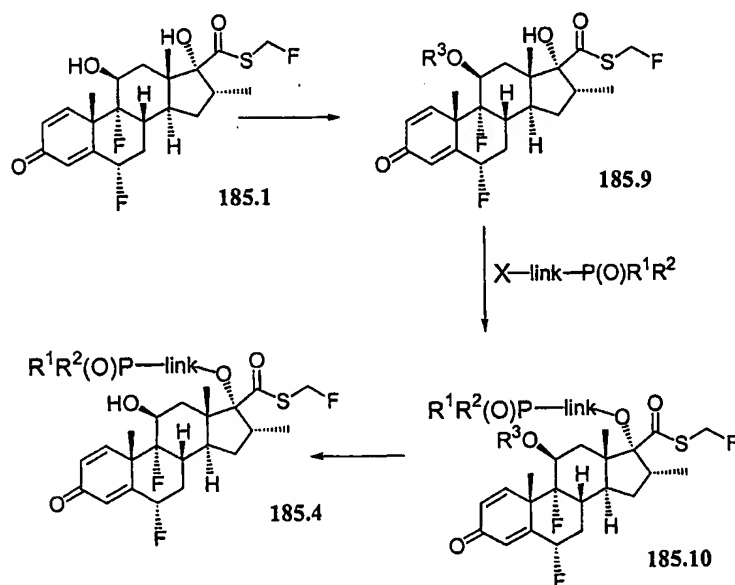
Representative compounds of the invention can be prepared as illustrated above.

The less sterically hindered C-11 hydroxy group of compound **184.1** is selectively alkylated with the appropriate phosphonate to give analogs of formula **184.3**. A specific compound of the invention can be prepared as follows.



After regioselective extraction of the C-11 hydroxy proton in **184.1** using one equivalent of sodium hydride, the phosphonate triflate is added to provide the ether **184.8**.

Example 185 Preparation of Representative Compounds of the Invention



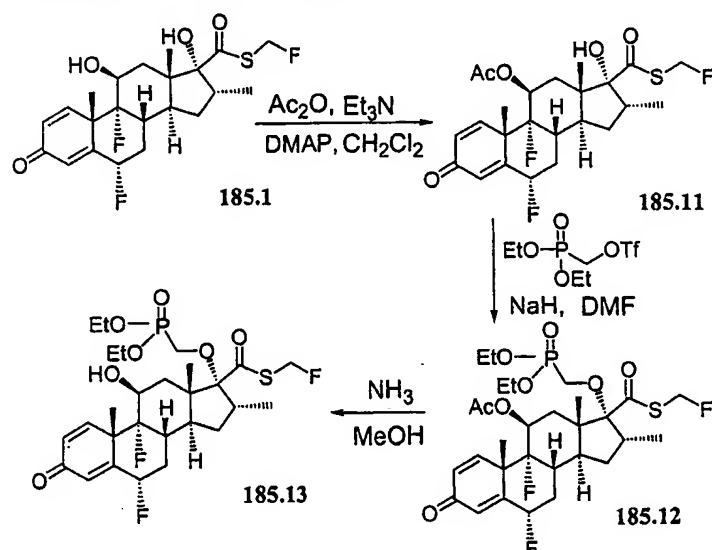
Representative compounds of the invention can be prepared as illustrated above.

Again taking advantage of the reactivity difference between C-11 and C-17 hydroxy groups, the C-11 hydroxy group is masked by an appropriate protecting group.

After alkylation at the C-17 hydroxy moiety of **185.9** with a leaving

5 group-attached phosphonate and subsequent deprotection, desired analog **185.4**

is obtained. A specific compound of the invention can be prepared as follows.

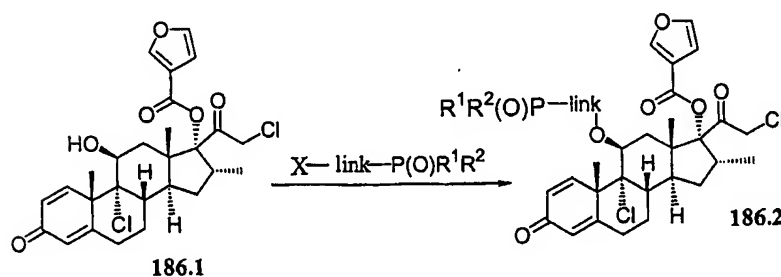


Fluticasone **185.1** is regioselectively protected as its C-11 acetate ester using the standard acetic anhydride and DMAP conditions. (*J. Org. Chem.* 1998, 63,

10 2342-2347) Alkylation at the exposed C-17 hydroxy group with sodium hydride and the phosphonate triflate furnishes the intermediate **185.12**. Final ammonia deprotection of the acetate affords the desired ether **185.13**.

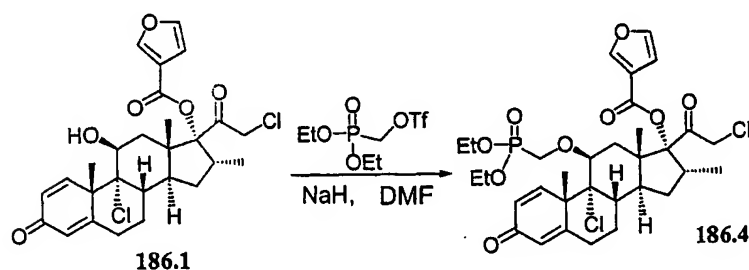
Example 186 Preparation of Representative Compounds of the Invention

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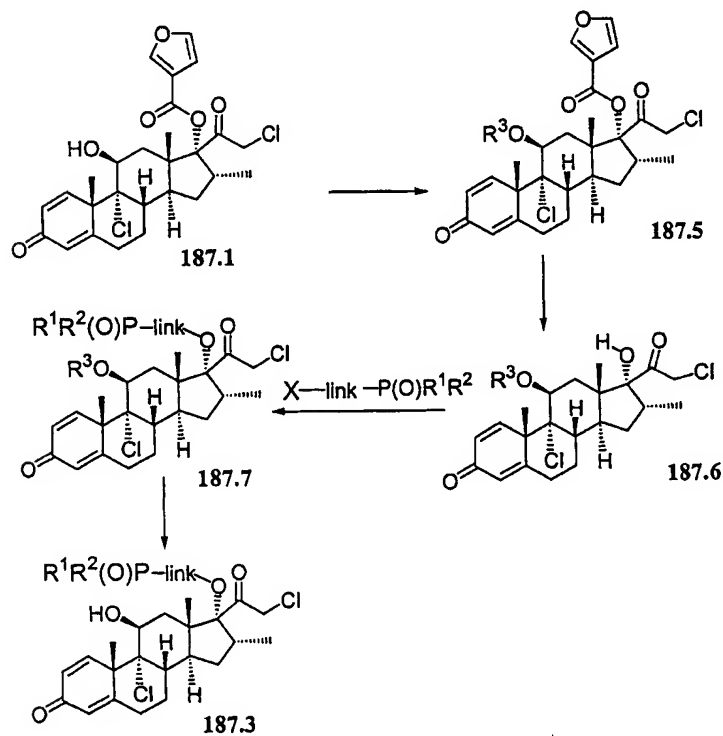
Representative compounds of the invention can be prepared as illustrated above. Derivatization at the C-11 hydroxy group is accomplished through alkylation of mometasone furate **186.1** with the appropriate phosphonate, furnishing analogs of formula **186.2**. A specific compound of the invention can

5 be prepared as follows.

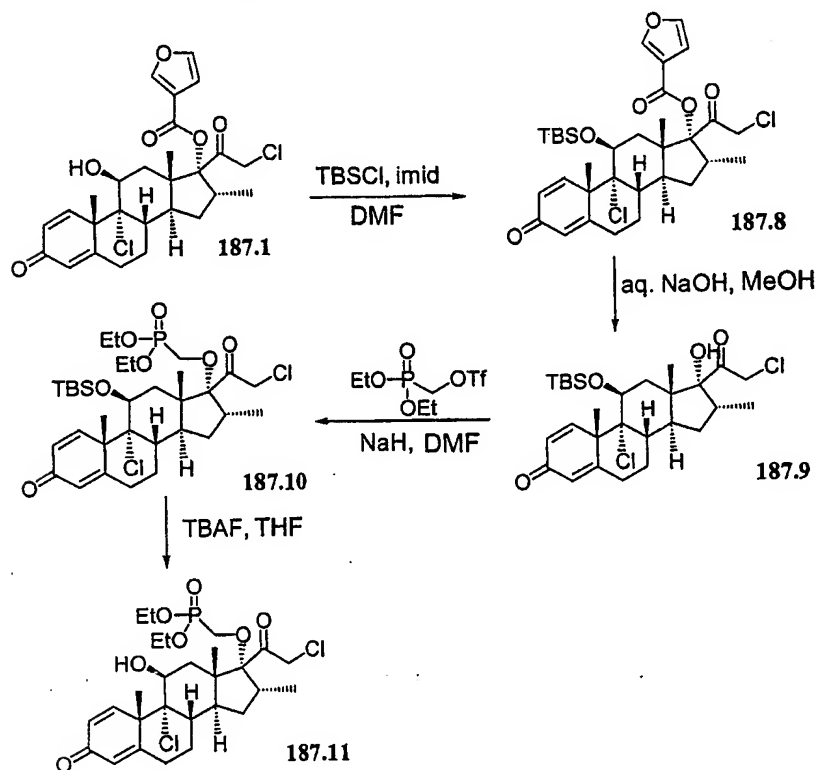


After sodium hydride extraction of the hydroxy proton in **186.1**, diethyl
10 phosphonate triflate is added to afford ether **186.4**.

Example 187 Preparation of Representative Compounds of the Invention

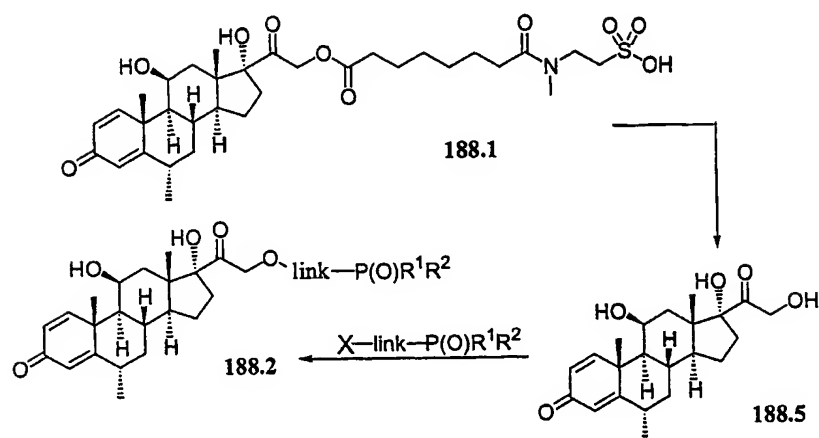


Representative compounds of the invention can be prepared as illustrated above. Following protection of the only exposed hydroxy group in mometasone fuorate **187.1**, intermediate **187.5** is saponified to give alcohol **187.7**. Alkylation at the C-17 hydroxy group with the appropriate phosphonate and subsequent deprotection provides the desired product **187.3**. A specific compound of the invention can be prepared as follows.



Mometasone fuorate **187.1** is protected as its silyl ether using the standard TBSCl and imidazole conditions (*J. Am. Chem. Soc.* 1972, 94, 6190). Saponification of the fuoryl ester moiety using aqueous sodium hydroxide provides the alcohol **187.9**. (*J. Chem. Soc. Perkin Trans. 1* 1993, 12, 1359-1366) The tertiary hydroxy group is alkylated by the addition of sodium hydroxide and the phosphonate triflate. After deprotection of the silyl ether in intermediate **187.10** with TBAF, diethyl phosphonate **187.11** results.

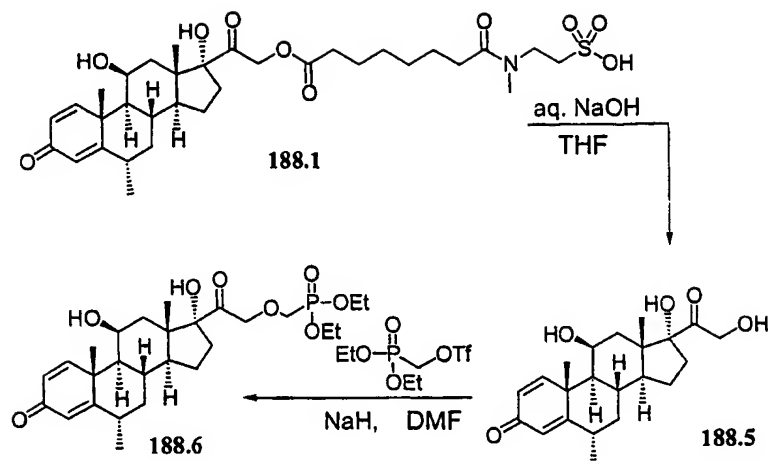
Example 188 Preparation of Representative Compounds of the Invention



5

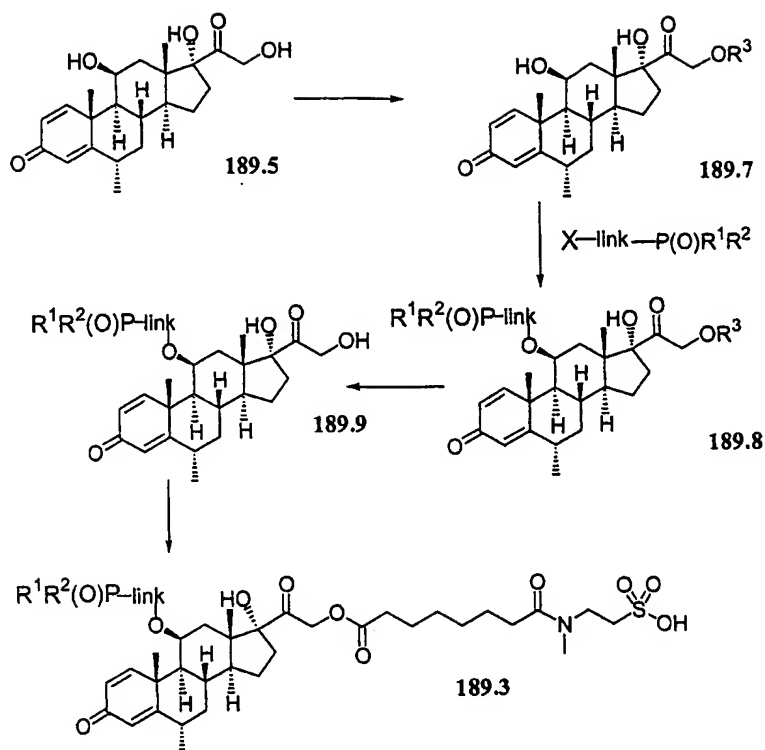
Representative compounds of the invention can be prepared as illustrated above. Since the sodium sulfonate moiety in methylprednisolone suleptanate 188.1 is the most nucleophilic site in the molecule, syntheses of analogs typically involve protection of or late stage installation of the sulfonate functional group. To employ the latter strategy, 188.1 is first saponified to furnish the triol 188.5. Alkylation at the primary hydroxy group with the appropriate phosphonate furnishes analogs of formula 188.2. A specific compound of the invention can be prepared as follows.

15

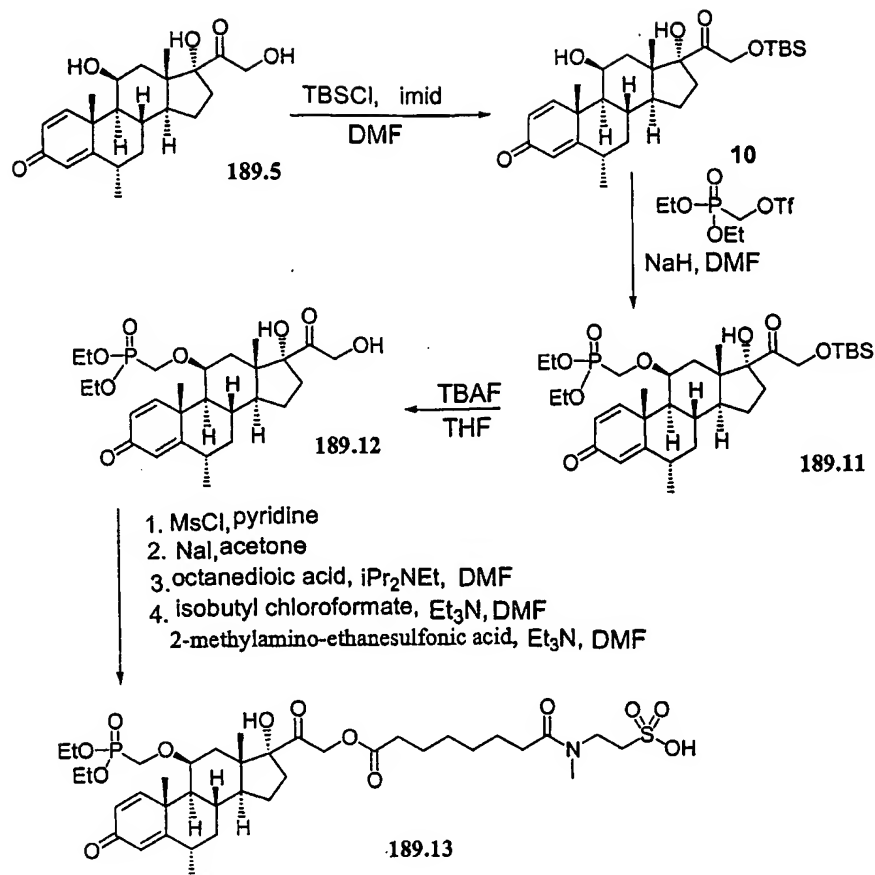


- Hydrolysis of the suleptanate ester in **188.1** is accomplished by using aqueous sodium hydroxide, producing the triol **188.5**. The less sterically hindered primary hydroxy group is alkylated by the addition of sodium hydroxide and the phosphonate triflate, giving diethyl phosphonate **188.6**.

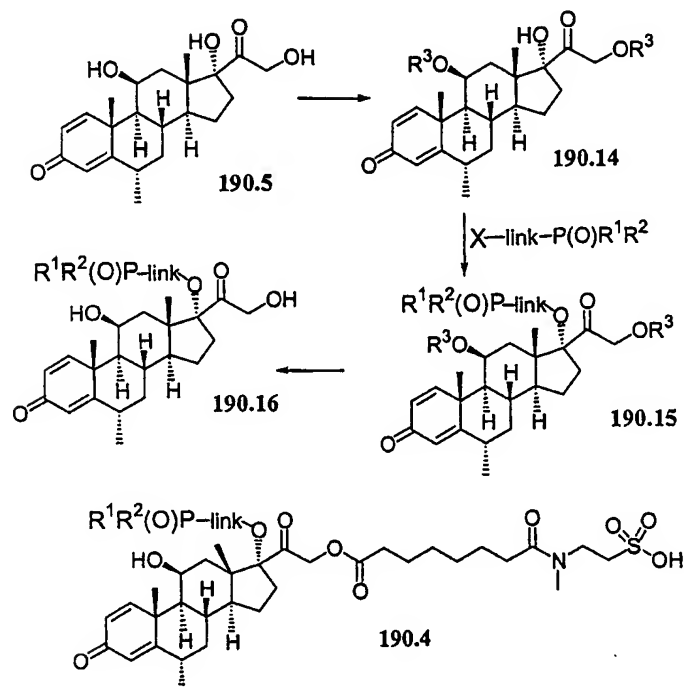
Example 189 Preparation of Representative Compounds of the Invention



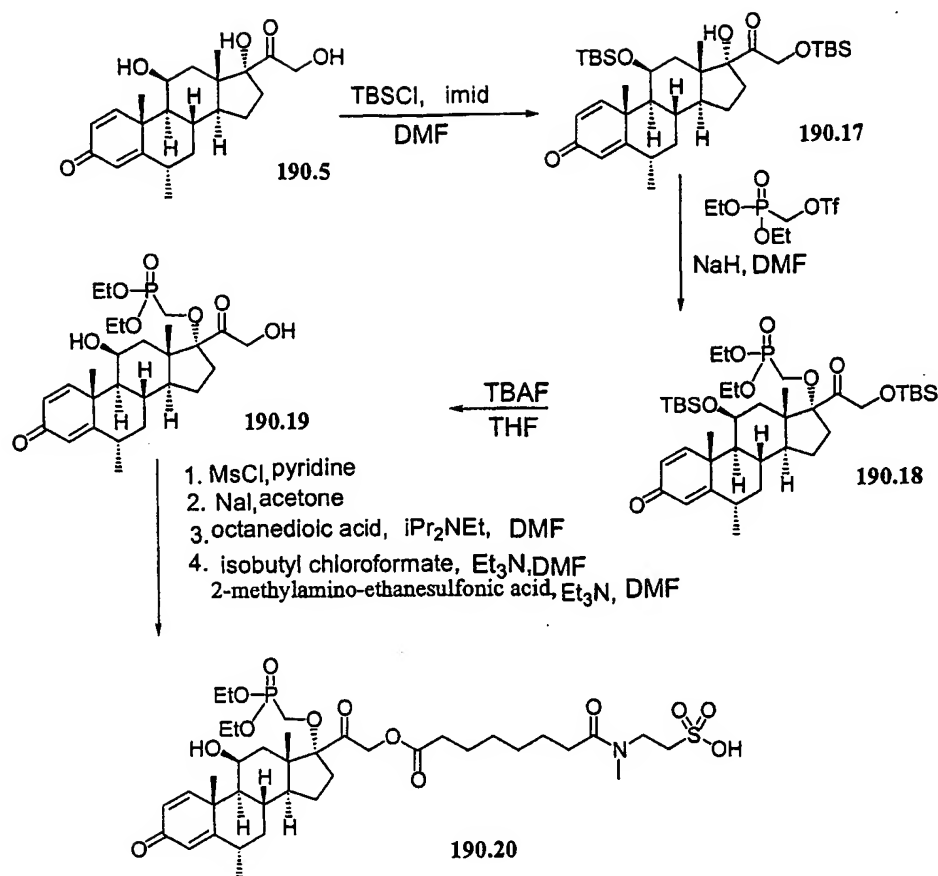
Representative compounds of the invention can be prepared as illustrated above. Following protection of the primary hydroxy group, protected
 5 intermediate 189.7 is alkylated at the more exposed C-11 hydroxy site. Deprotection and subsequent installation of the suleptanate ester provides the desired product 189.3. A specific compound of the invention can be prepared as follows.



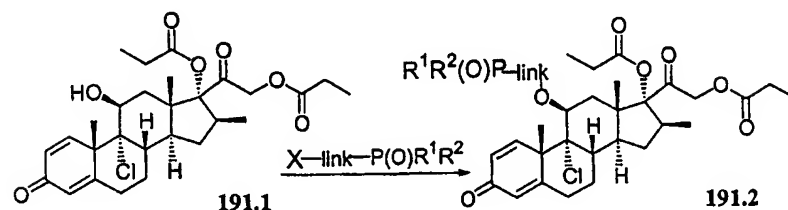
Triol **189.5** is protected as its silyl ether using the standard TBSCl and imidazole conditions. (*J. Am. Chem. Soc.* 1972, 94, 6190) After alkylating with the diethyl phosphonate triflate, the resulting intermediate **189.11** is treated with TBAF to give the diol **189.12**. Attachment of the suleptanate ester is accomplished in four steps: activation of the primary alcohol as its mesylate, Finkelstein conversion to the iodide (*Tetrahedron Lett.* 1981, 22, 2055), nucleophilic substitution with octanedioic acid, and final activation and displacement with the secondary amine provides compound **189.13**. (*J. Pharm. Sci.* 1985, 74, 365-374).

Example 190 Preparation of Representative Compounds of the Invention

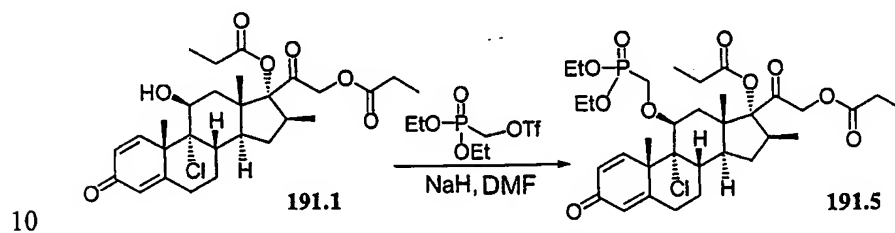
- 5 Representative compounds of the invention can be prepared as illustrated above. Protection of triol 190.5 at the two less hindered sites furnishes alcohol 190.14, which is alkylated at the only exposed hydroxy group with the appropriate phosphonate. Deprotection and formation of the suleptanate ester completes the synthesis of analog 190.4. A specific compound of the invention
- 10 can be prepared as follows.



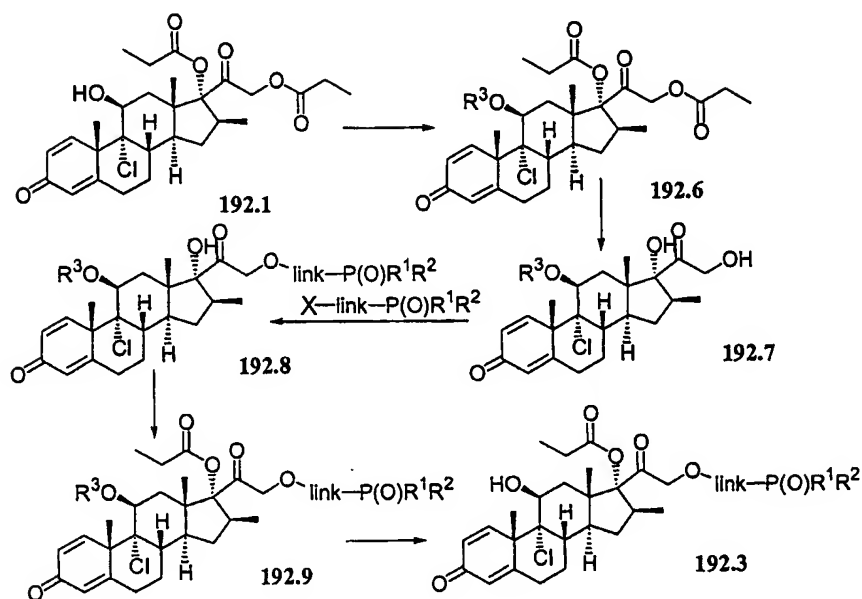
- Triol **190.5** is protected as its TBS ether; however, harsher conditions
 5 should allow for bis-protection. After alkylating with the diethyl phosphonate
 triflate, the resulting intermediate **190.18** is treated with TBAF to give the diol
190.19. Attachment of the suleptanate ester is accomplished in four steps:
 activation of the primary alcohol as its mesylate, Finkelstein conversion to the
 iodide (*Tetrahedron Lett.* 1981, 22, 2055), nucleophilic substitution with
 10 octanedioic acid, and final activation and displacement with the secondary amine
 provides compound **190.20**. (*J. Pharm. Sci.* 1985, 74, 365-374)

Example 191 Preparation of Representative Compounds of the Invention

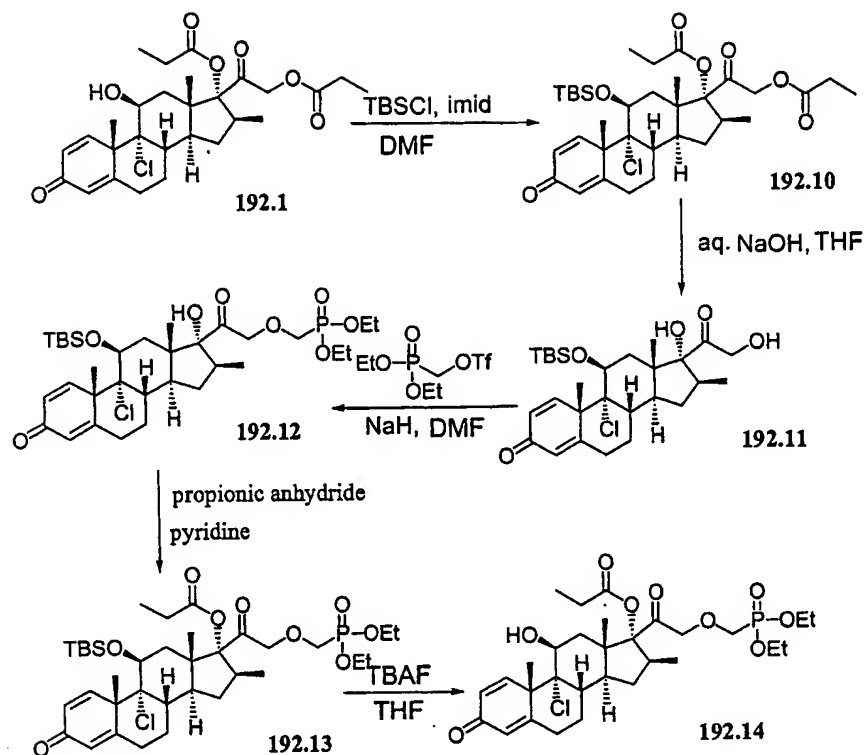
5 Representative compounds of the invention can be prepared as illustrated above. Derivatization at the C-11 hydroxy group is accomplished through alkylation of beclomethasone 191.1 with the appropriate phosphonate, furnishing analogs of formula 191.2. A specific compound of the invention can be prepared as follows.



10 After sodium hydride extraction of the hydroxy proton in compound 191.1, diethyl phosphonate triflate is added to afford ether 191.5.

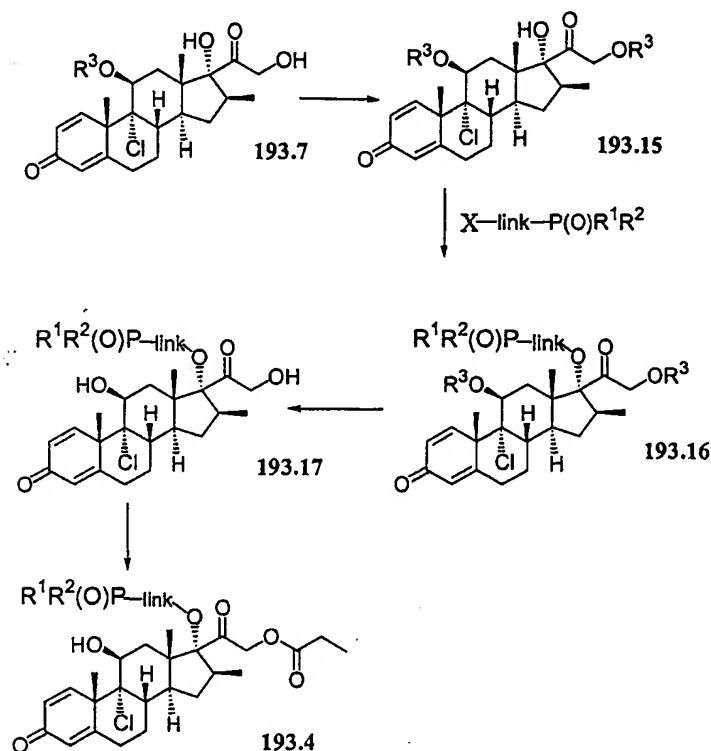
Example 192 Preparation of Representative Compounds of the Invention

- 5 Representative compounds of the invention can be prepared as illustrated above by exploiting the reactivity differences among the three hydroxy groups available when beclomethasone 192.1 is fully hydrolyzed. Following protection of the only exposed hydroxy group in 192.1, intermediate 192.6 is saponified to give diol 192.7. Alkylation at the primary hydroxy group with the appropriate
- 10 phosphonate and subsequent acylation provides the propionate ester 192.9. The desired product 192.3 is achieved after deprotection. A specific compound of the invention can be prepared as follows.

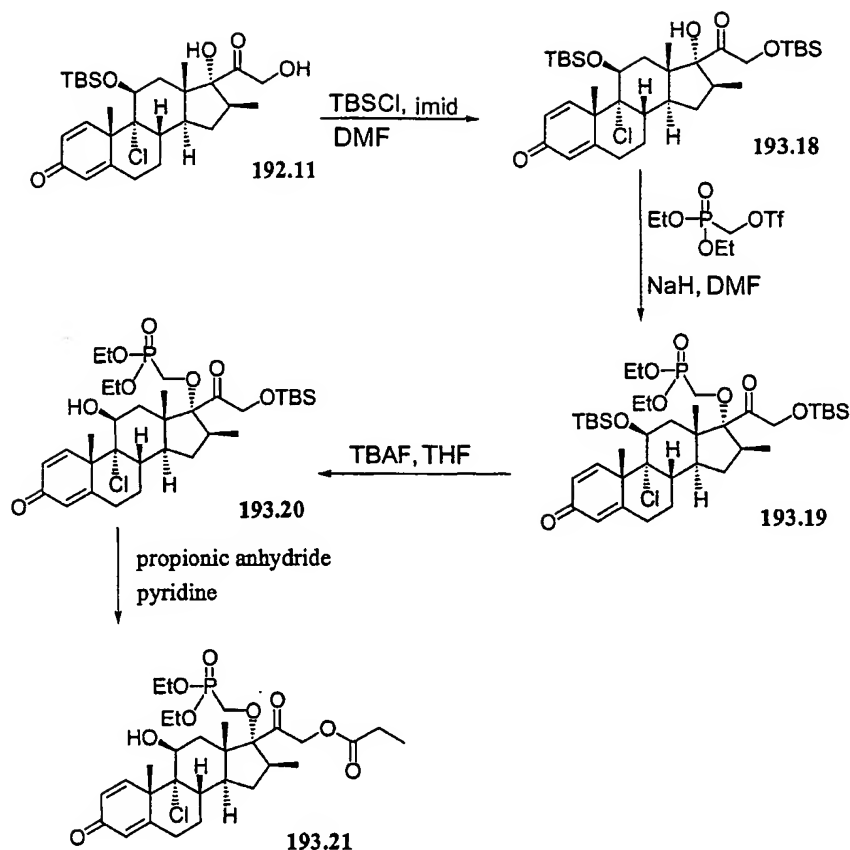


Beclamethasone **192.1** is protected as its silyl ether using the standard TBSCl and imidazole conditions (*J. Am. Chem. Soc.* **1972**, *94*, 6190).

- 5 Saponification of both propionic ester moieties using aqueous sodium hydroxide provides the diol **192.11**. The less sterically hindered primary hydroxy group is alkylated by the addition of sodium hydroxide and the phosphonate triflate. After treating intermediate **192.12** with propionic anhydride in pyridine, the previously hydrolyzed C-17 propionic ester is replaced. (*J. Med. Chem.* **1980**,
 10 **23**, 430-437) TBAF deprotection of the silyl ether furnishes diethyl phosphonate **192.14**.

Example 193 Preparation of Representative Compounds of the Invention

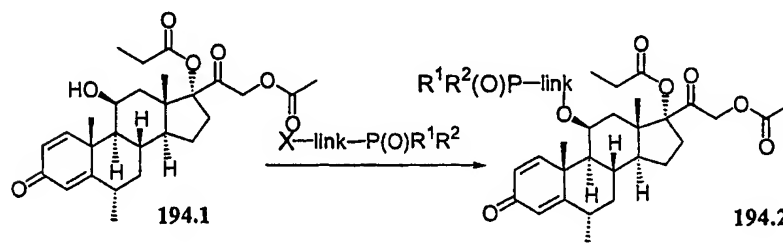
Representative compounds of the invention can be prepared as illustrated
 5 above. The two hydroxy groups of diol 193.7 are regioselectively differentiated
 by protection at the primary site, thus allowing alkylation at the tertiary hydroxy
 group. The resulting phosphonate intermediate 193.16 is then deprotected to
 afford the diol 193.17. The more accessible primary hydroxy group is acylated
 to produce the desired analog 193.4. A specific compound of the invention can
 10 be prepared as follows.



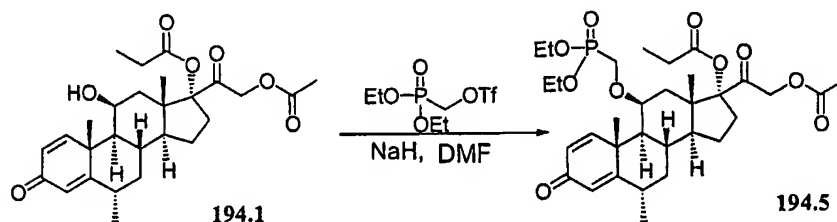
Diol **192.11** (see Example 192) is protected at the primary site as its silyl ether **193.18**. Following alkylation with the diethyl phosphonate triflate, the resulting intermediate **193.19** is treated with TBAF to give diol **193.20**. Propionic anhydride and pyridine are used to generate the final product **193.21**. (*J. Med. Chem.* 1980, 23, 430-437)

Example 194 Preparation of Representative Compounds of the Invention

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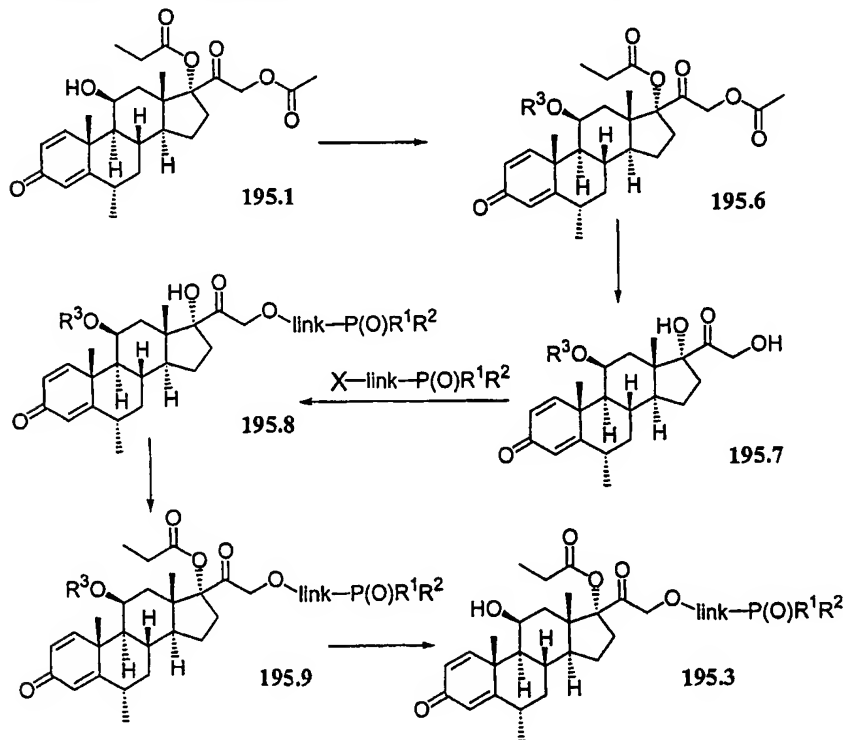


Representative compounds of the invention can be prepared as illustrated above. Derivatization at the C-11 hydroxy group is accomplished through alkylation of methylprednisolone aceponate **194.1** with the appropriate phosphonate, furnishing analogs of formula **194.2**. A specific compound of the invention can be prepared as follows.

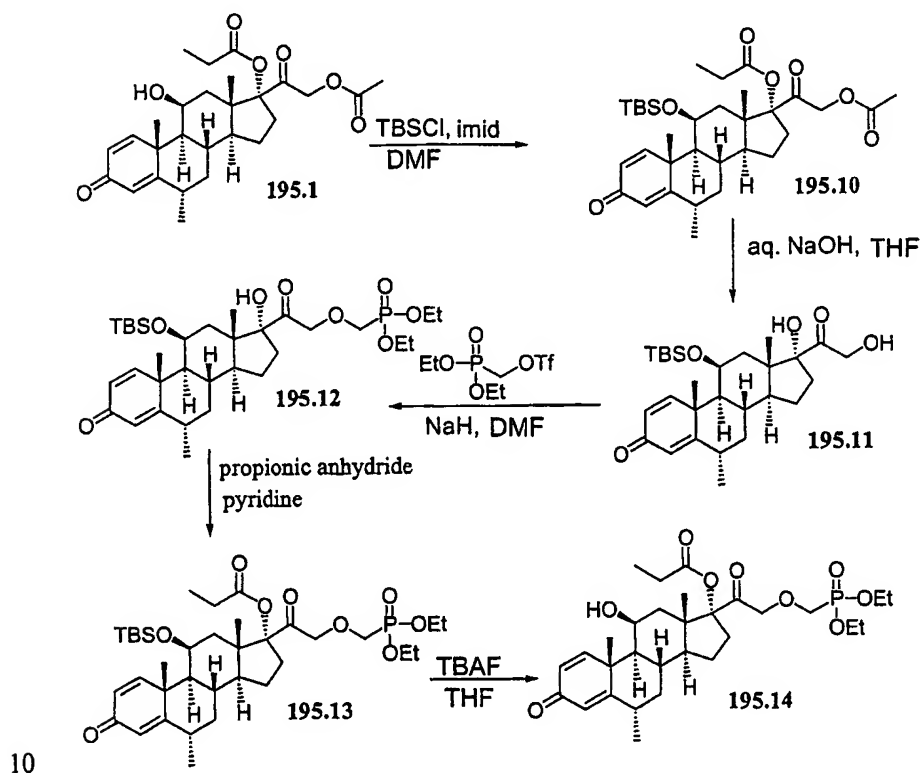


After sodium hydride extraction of the hydroxy proton in **194.1**, diethyl phosphonate triflate is added to afford ether **194.5**.

Example 195 Preparation of Representative Compounds of the Invention



Representative compounds of the invention can be prepared as illustrated above by exploiting the reactivity differences among the three hydroxy groups available when methylprednisolone aceponate **195.1** is fully hydrolized. Following protection of the only exposed hydroxy group in **195.1**, intermediate **195.6** is saponified to give diol **195.7**. Alkylation at the primary hydroxy group with the appropriate phosphonate and subsequent acylation provides the propionate ester **195.9**. The desired product **195.3** is achieved after deprotection. A specific compound of the invention can be prepared as follows.

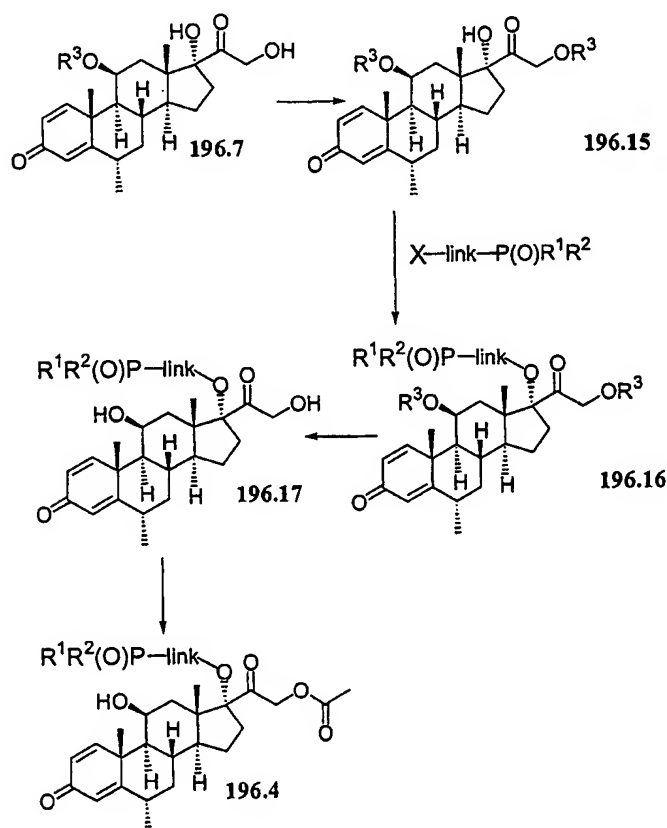


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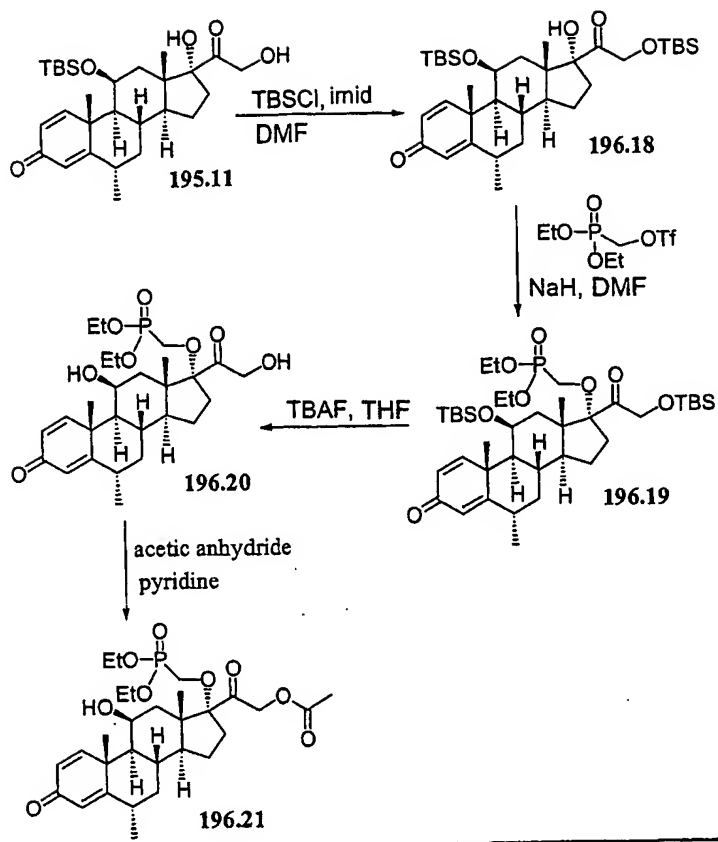
Methylprednisolone aceponate **195.1** is protected as its silyl ether using the standard TBSCl and imidazole conditions. (*J. Am. Chem. Soc.* 1972, 94, 6190). Saponification of both ester moieties using aqueous sodium hydroxide provides the diol **195.11**. The less sterically hindered primary hydroxy group is alkylated by the addition of sodium hydroxide and the phosphonate triflate. After treating intermediate **195.12** with propionic anhydride in pyridine, the

previously hydrolyzed C-17 propionic ester is replaced. (*J. Med. Chem.* 1980, 23, 430-437) TBAF deprotection of the silyl ether furnishes diethyl phosphonate **195.14**.

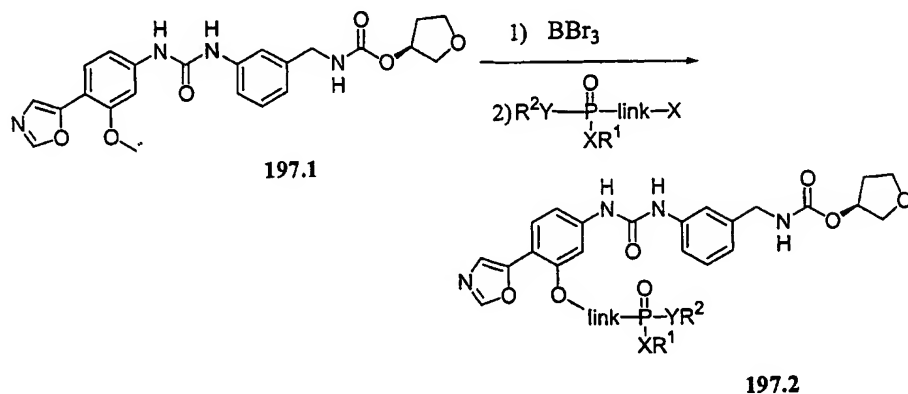
5 Example 196 Preparation of Representative Compounds of the Invention



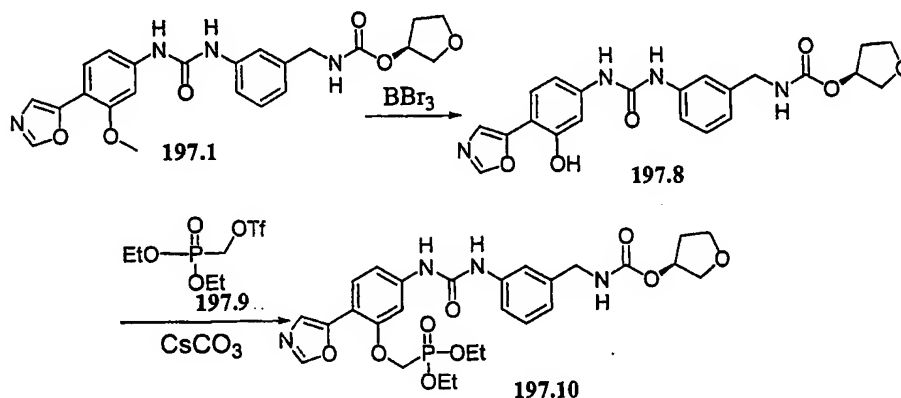
Representative compounds of the invention can be prepared as illustrated
 10 above. The two hydroxy groups of diol **196.7** are regioselectively differentiated
 by protection at the primary site, thus allowing alkylation at the tertiary hydroxy
 group. The resulting phosphonate intermediate **196.16** is then deprotected to
 afford the diol **196.17**. Again the more accessible primary hydroxy group is
 acylated to produce the desired analog **196.4**. A specific compound of the
 15 invention can be prepared as follows.



Diol **195.11** (see example 195) is protected at the primary site as its silyl ether **196.18**. Following alkylation with the diethyl phosphonate triflate, the
5 resulting intermediate **196.19** is treated with TBAF to give diol **196.20**. Acetic anhydride and pyridine are used to generate the final product **196.21**. (*J. Mol. Biol.* 1972, 72, 219).

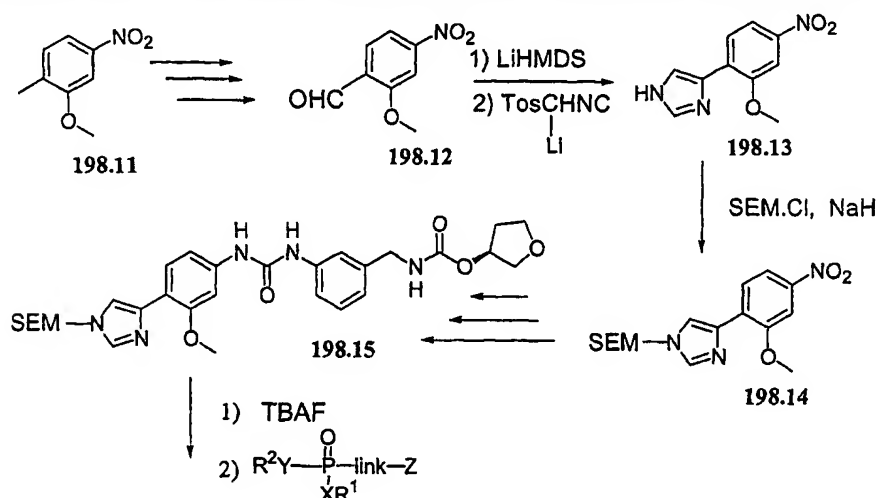
Example 197 Preparation of Representative Compounds of the Invention

- 5 Representative compounds of the invention can be prepared as illustrated above. The phosphorus containing merimepodib analog **197.2** is synthesized from parent compounds by alkylation. Merimepodib **197.1** is obtained by the procedure as described in US 6054472 and US 6344465. The methoxy group of merimepodib **197.1** is demethylated to phenolic OH using a suitable reagent,
- 10 such as boron tribromide. The phosphonate moiety is introduced to the phenolic OH in a suitable aprotic solvent such as, DMF and is then treated with the phosphonate reagent bearing a leaving group, for example, bromine, mesyl, tosyl, or trifluoromethanesulfonyl, in the presence of a suitable organic or inorganic base. A specific compound of the invention can be prepared as
- 15 follows.



- A solution of **197.1** in dichloromethane is treated with boron tribromide to obtain the demethylated compound **197.8**. Compound **197.8** is then treated with cesium carbonate and one equivalent of (trifluoromethanesulfonyloxy)-methylphosphonic acid diethyl ester **197.9** to give merimepodib-phosphonate **197.10**. Using the above procedure but employing different phosphonate reagents, the corresponding products **197.2** bearing different linking group can be obtained.

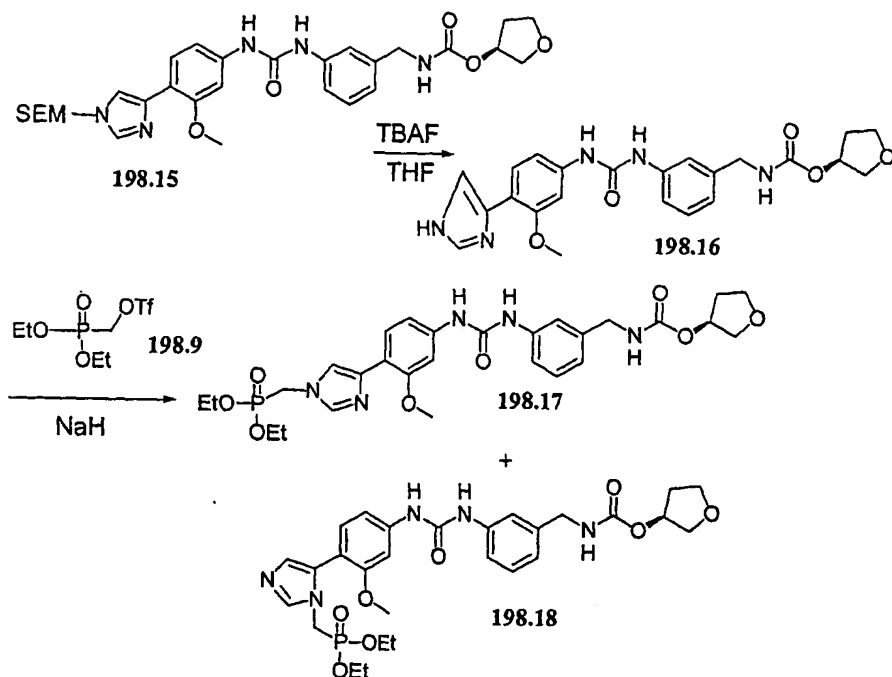
Example 198 Preparation of Representative Compounds of the Invention



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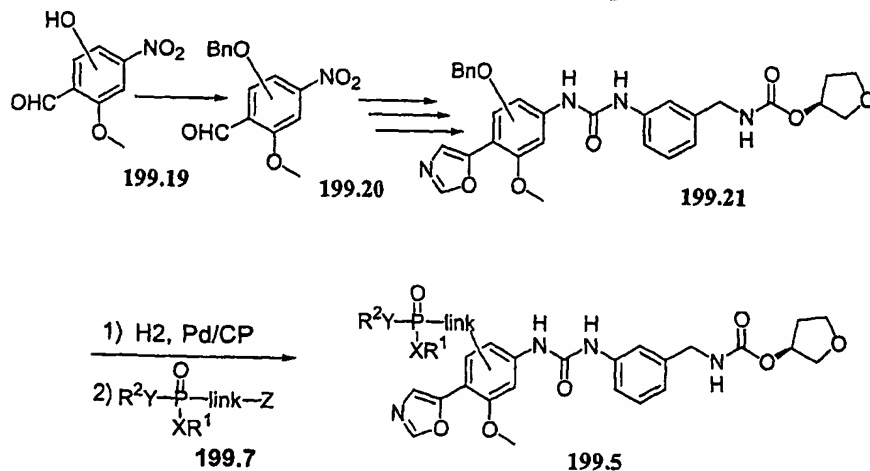
- Representative compounds of the invention can be prepared as illustrated above. The imidazole containing intermediate **198.13** is synthesized from an aldehyde **198.12** by the procedure of Shih in *Tetrahedron Lett.* **1993**, *34*, 595. Compound **198.12** is prepared by a two-step procedure described in US5807876, US6054472, and US6344465. The imidazole is protected using suitable reagent, for example 2-(trimethylsilyl)ethoxymethyl (SEM) chloride, and the compound **198.14** is converted to **198.15** by the similar procedure described for the synthesis of **197.1** in US6054472 and US6344465. After the protecting group on the imidazole of **198.15** is removed, the phosphonate containing moiety is introduced to the imidazole to provide compounds of the invention. A specific compound of the invention can be prepared as follows.

20

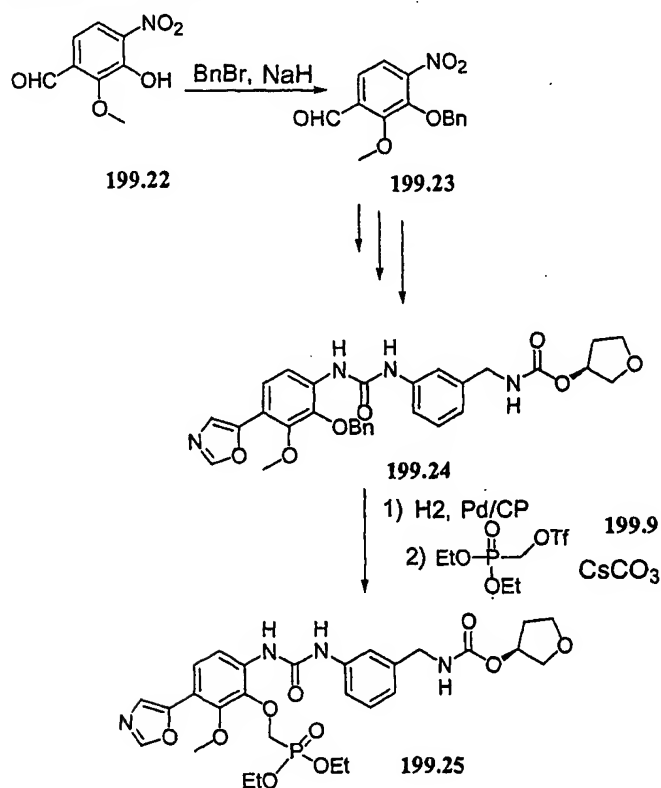


Compound 198.15 is treated with tetrabutylammonium fluoride in THF in reflux condition and the resulting 198.16 is alkylated with 198.9 using sodium hydride as a base to obtain two isomers 198.17 and 198.18, which are separated by chromatography.

Example 199 Preparation of Representative Compounds of the Invention



Representative compounds of the invention can be prepared as illustrated above. Tetrasubstituted benzene derivatives are obtained by literature procedures (Ichikawa and Ichibagase *Yakugaku Zasshi* 1963, 83, 103; Norio, A. *et al. Tetrahedron Lett.* 1992, 33(37), 5403). After the phenolic OH is protected with a suitable protecting group, for example benzyl group, the compound 199.21 is synthesized by the same procedure described in US6054472, and US 6344465. After the protecting group is removed, the phosphonate containing moiety is introduced to the phenolic OH using the phosphonate reagent 199.7, bearing a suitable leaving group. A specific compound of the invention can be prepared as follows.

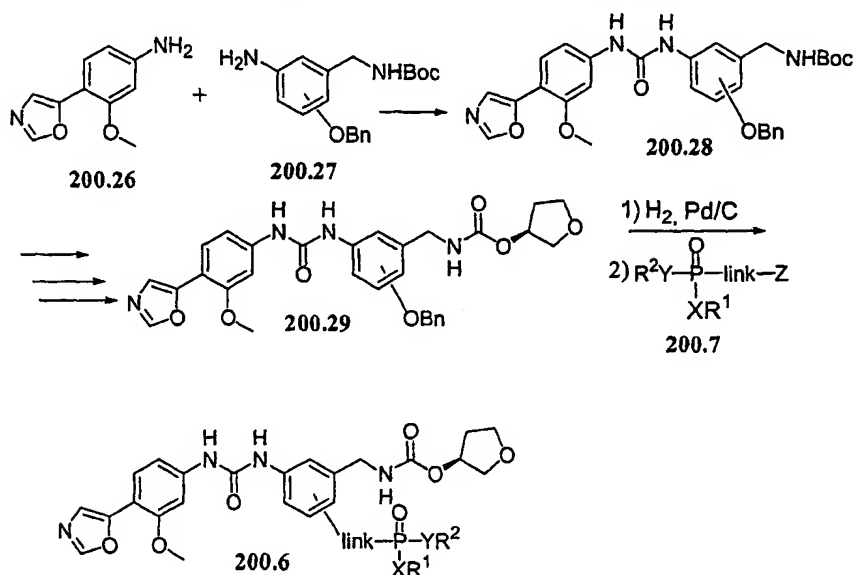


For example, a solution of 199.22, which is obtained by the procedure of Norio et al. (*Tetrahedron Lett.* 1992, 33(37), 5403), is treated with sodium hydride and one equivalent of benzyl bromide in DMF to get 199.23. Compound 199.23 is converted to 199.24 by a series of steps such as those reported in US6054472, and US6344465. After the benzyl protecting group of

199.24 is removed by catalytic hydrogenation, a phosphonate bearing moiety is attached by alkylation of the resulting phenol in DMF using sodium hydride and one equivalent of (trifluoromethanesulfonyloxy)methylphosphonic acid diethyl ester 199.9 to give 199.25.

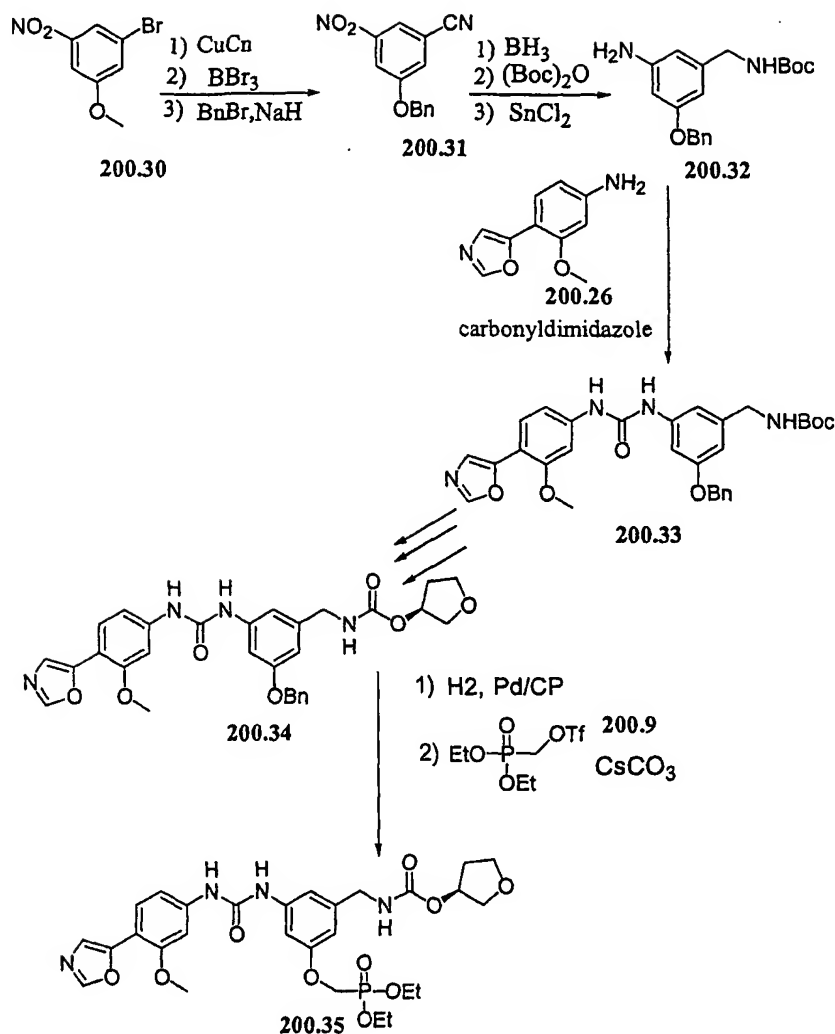
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Example 200 Preparation of Representative Compounds of the Invention



Representative compounds of the invention can be prepared as illustrated above. Compound 200.26 is treated with carbonyldiimidazole or triphosgene followed by the compound 200.27, which has a handle to attach phosphonate moiety. Compound 200.27 bearing an extra substituent is synthesized from the tri substituted phenol with a cyano and a nitro groups, which is either commercially available or by literature procedures (Zolfigol, M. A. *et. al. Indian J. Chem. Sect. B* 2001, 40, 1191; De Jongh, R. O. *et al. Recl. Trav. Chim. Pays-Bas* 1968, 87, 1327). The resulting 200.28 is converted to 200.29 using procedures similar to those described in US6054472, and US 6344465. The phosphonate moiety of 200.6 is attached after deprotection of the benzyl group of 200.29.

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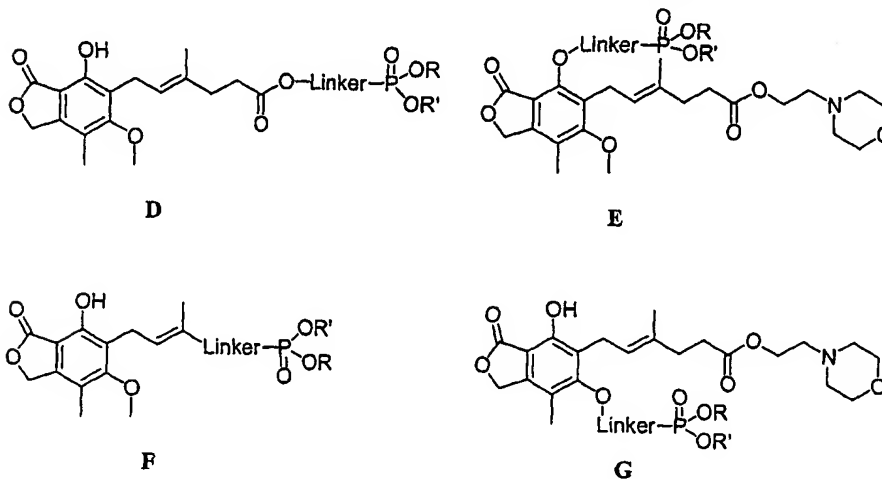
- For example, the bromine substituent of compound 200.30 is substituted with cyano group by the procedure of De Jongh, R. O. *et al.* (*Recl. Trav. Chim. Pays-Bas* **1968**, 87, 1327) and the methoxy group is converted to benzyloxy group as a protecting group, which affords compound 200.31. After selective reduction of cyano to aminomethyl group by borane, the amino group is protected with Boc group and then the reduction of the nitro group using tin (II) chloride generates compound 200.32. This substituted aniline 200.32 is then treated with a reaction mixture of the compound 200.26 and carbonyldiimidazole, as described in US6054472, and US 6344465, to form the urea 200.33. Compound 200.33 is converted to 200.34. Deprotection of the

benzyl group using catalytic hydrogenation followed by attachment of a phosphonate moiety using **200.9** in the presence of cesium carbonate produces compound **200.35**.

5

Examples 201-204

Representative compounds of the invention having the following formulae can be prepared as described in Examples 201-204.

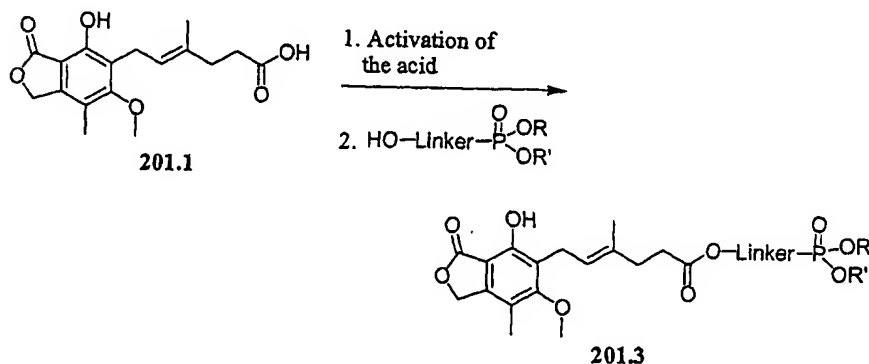


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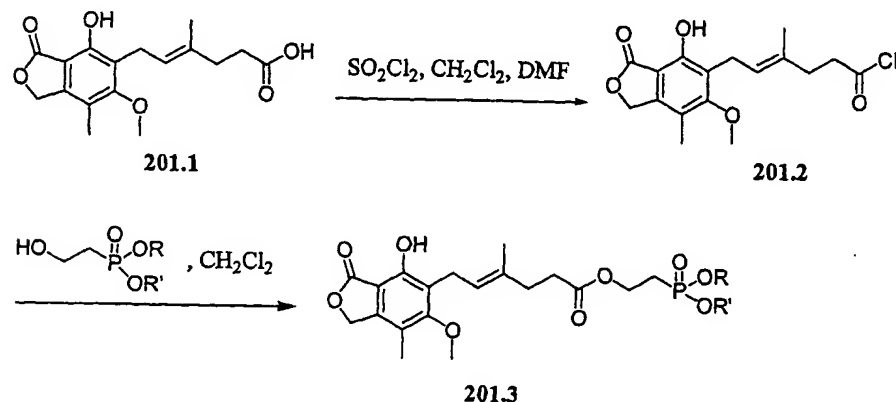
For example, three regions of mycophenolate mofetil can be utilized for the attachment of the phosphonate prodrug as demonstrated by compounds **D**, **E**, and **G** shown above. Also, the carboxylic acid can be replaced with a phosphonic acid as in compound **F**.

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Example 201 Preparation of Representative Compounds of the Invention

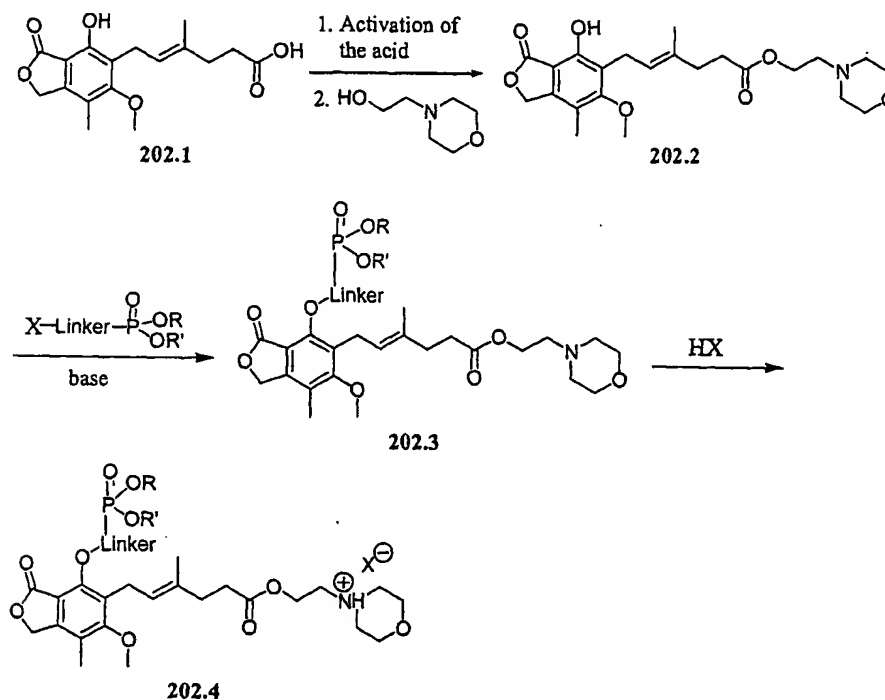


Representative compounds of the invention can be prepared as illustrated above. The morpholino ethyl moiety can serve as a prodrug functionality to improve bioavailability and can be replaced with the phosphonate prodrug handle as shown above. Mycophenolic acid is commercially available, e.g., from Sigma Chemical Company, St. Louis, Mo. Activation of the carboxylic acid **201.1** in the presence of the free phenol, followed by addition of an alcohol carrying the phosphonate group, results in the formation of the desired product **201.3** (US 4,786,637). A specific compound of the invention can be prepared as follows.



Mycophenolic acid **201.1** is dissolved in dichloromethane. Thionyl chloride is added followed by a catalytic amount of DMF. The reaction mixture is stirred at room temperature for 3 hours, after which the volatile components are removed under vacuum. The phosphonate-alcohol is dissolved in dichloromethane and chilled to about 4 °C on an ice bath. The mycophenolic acid chloride **201.2** is dissolved in dichloromethane and added to the chilled solution. After stirring for 90 minutes at about 4 °C, the reaction mixture is washed with water and then with aqueous sodium bicarbonate. The organic solution is dried and evaporated to yield the phosphonate **201.3**.

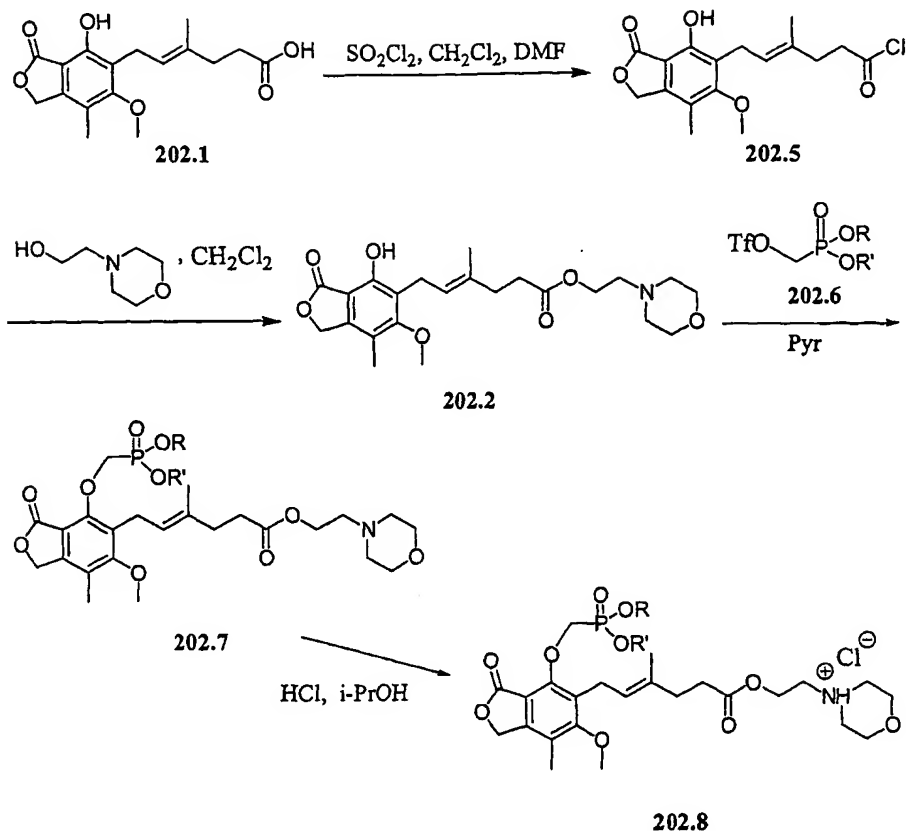
Example 202 Preparation of Representative Compounds of the Invention



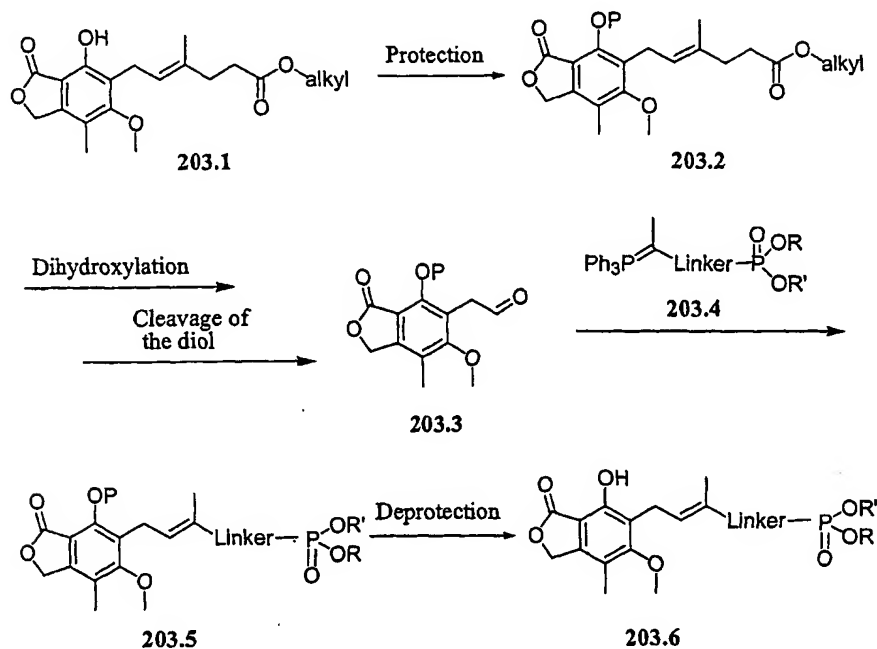
5 Representative compounds of the invention can be prepared as illustrated above. The C-4 phenol position provides a reactive handle for further analogs as illustrated above. Once the carboxylic acid of **202.1** is blocked by morpholino ethyl, such as in compound **202.2** the phenol can be alkylated under basic conditions. Bases such as pyridine, potassium carbonate, or triethylamine are

10 utilized. Leaving groups such as trifluoromethylsulfonate, mesylate, bromide, or iodide are attached to the phosphonate prodrug subunit and reacted, in the presence of base, with compound **202.2**. Compound **202.3** can either be used directly, or in the form of a salt, compound **202.4**. Among the large number of salts that can be prepared, chloride and bisulfate salts are one particular

15 embodiment of the invention. A specific compound of the invention can be prepared as follows.



- Compound **202.5** is prepared similar to compound **201.2** (described in Example 201). A solution of morpholino ethanol in dichloromethane is cooled to about 4 °C. The mycophenolic acid chloride **202.5** is dissolved in
- 5 dichloromethane and added to the cooled solution. Stirring this solution for about 90 minutes gives compound **202.2**. The reaction mixture is washed with water and dried with sodium sulfate. Removal of the solvent provides isolated compound **202.2**. Alkylation at the phenolic position of **202.2** is achieved by suspending the compound in pyridine. Triflate **202.6** is added to the solution
- 10 and the mixture is stirred at room temperature for about 90 minutes. The reaction mixture is poured into water and the product is extracted with ethyl acetate. Removal of the organic layer provides compound **202.7**. Hydrochloride salt of **202.7** can optionally be prepared. Compound **202.7** is dissolved in isopropanol and the solution is added to a mixture of hydrogen chloride in
- 15 isopropanol. The hydrochloride salt **202.8** is collected by filtration and dried under vacuum.

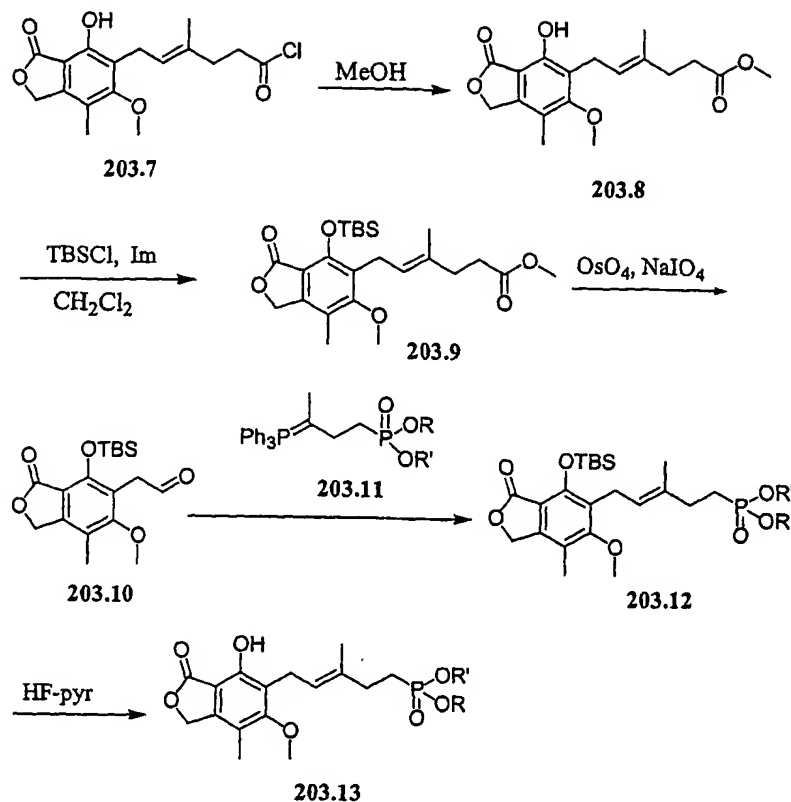
Example 203 Preparation of Representative Compounds of the Invention

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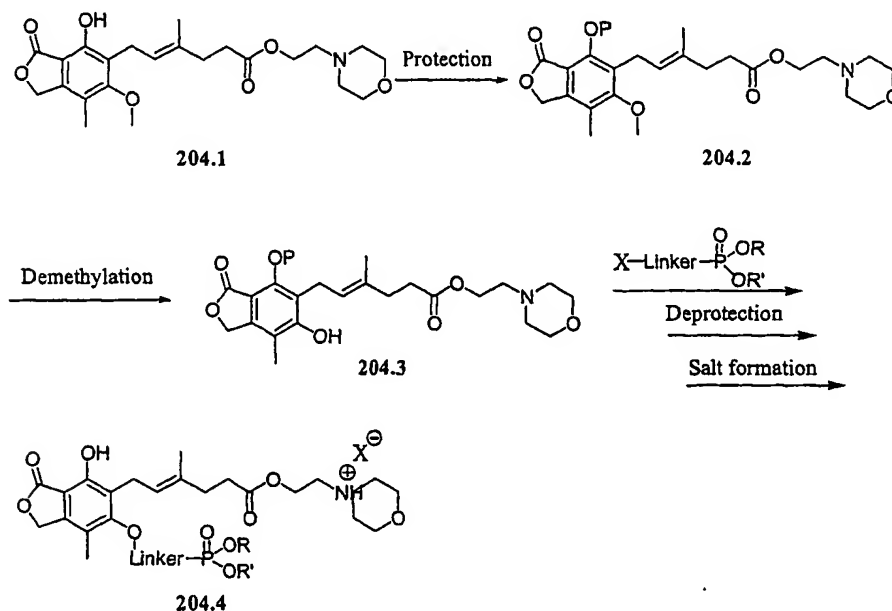
Representative compounds of the invention can be prepared as illustrated above. The carboxylic acid of mycophenolic acid can be replaced with a phosphonic acid that may also serve as a prodrug handle. In order to remove the carboxylic acid containing side chain, the acid chloride **202.5** (prepared in

10 Example 202) is converted to ester **203.1**. Protection of the phenol with a silyl group, followed by dihydroxylation and cleavage of the diol generates aldehyde **203.3** (Pankiewicz, et al., *J. Med. Chem.*, 2002, 45, 703), (Patterson et al., US 5,444,072) (Example 20). A Wittig reaction with ylide **203.4** carrying an appropriately protected phosphonate provides the desired compound **203.5**.

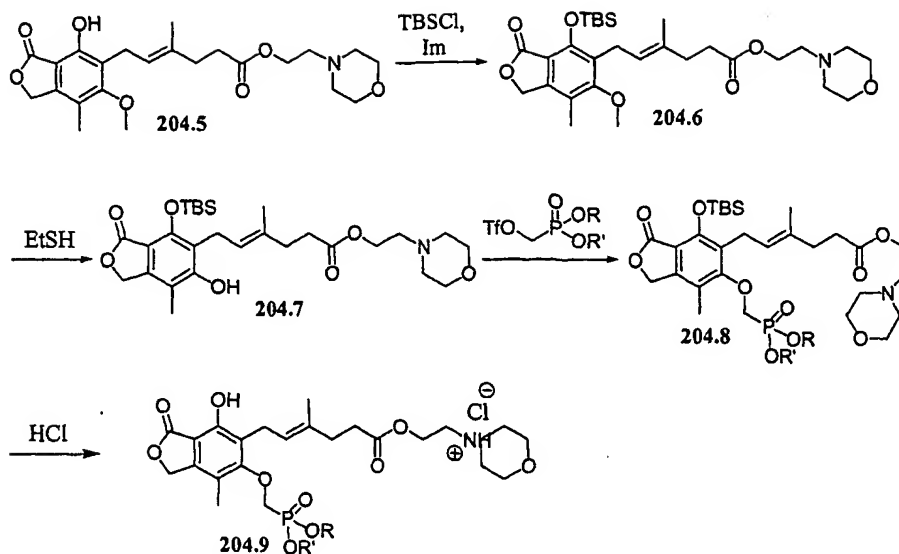
15 Final deprotection yields compound **203.6**. A specific compound of the invention can be prepared as follows.



- Mycophenolate ester **203.8** can simply be prepared by stirring the acid chloride **203.7** with MeOH. Then, the phenol position of mycophenolate ester is protected by a silyl group such as TBS to provide compound **203.9**. Once the phenol position is protected, dihydroxylation using osmium tetroxide followed by periodate cleavage provides aldehyde **203.10**. Aldehyde **203.10** and excess of the ylide **203.11** are heated in benzene at reflux for about 24 hours. The reaction mixture is concentrated and the residue is purified by column chromatography to provide olefin **203.12** (Pankiewics et al., *J. Med. Chem.*, 2002, 45, 703). A final deprotection using HF-pyridine yields the final product **203.13**.

Example 204 Preparation of Representative Compounds of the Invention

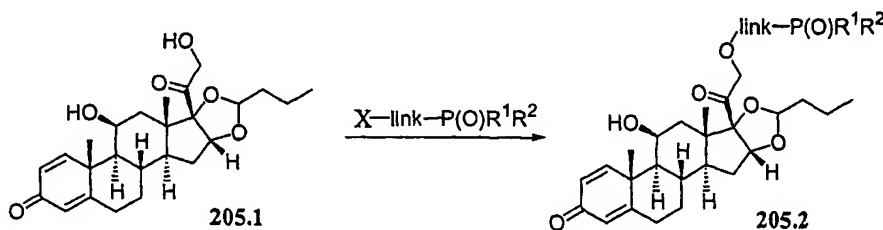
- 5 Representative compounds of the invention can be prepared as illustrated above. Another attachment point of the compound can be unmasked after demethylation of mycophenolate ester **204.2** as illustrated above. For this purpose, the 4-OH needs to be masked with a protecting group (P) such as a silyl group. Once the 6-MeO is demethylated and alkylated, the protecting group at position 4 is removed to reveal the final product **204.4**. The morphonyl ethanol
- 10 the morphonyl ethanol group is installed early and carried through the alkylation steps. A different protecting group may be installed initially and removed later. In such the latter type of synthesis, the last step is the formation of the morpholinoethyl ester prodrug. A specific compound of the invention can be prepared as described
- 15 below.



Phenol **204.5** is protected with TBS group in CH_2Cl_2 using imidazole as base to yield **204.6**. Demethylation is performed using thiolate nucleophiles to generate compound **204.7**. A variety of other methods are also available in literature as described in *Protective Groups in Organic Synthesis* by Greene and Wuts. Alkylation of the 6-OH using a triflate of the phosphonate proceeds well using K_2CO_3 or TEA to provide **204.8**. Final deprotection to remove the TBS group provides product **204.9**.

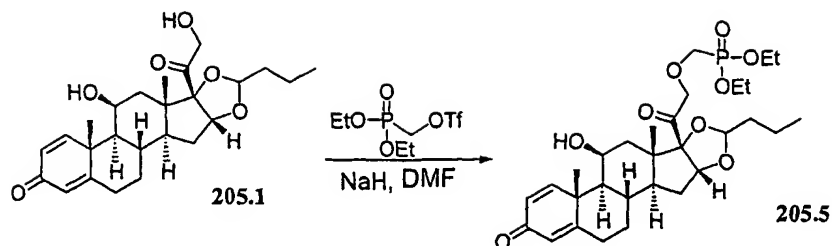
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Example 205 Preparation of Representative Compounds of the Invention



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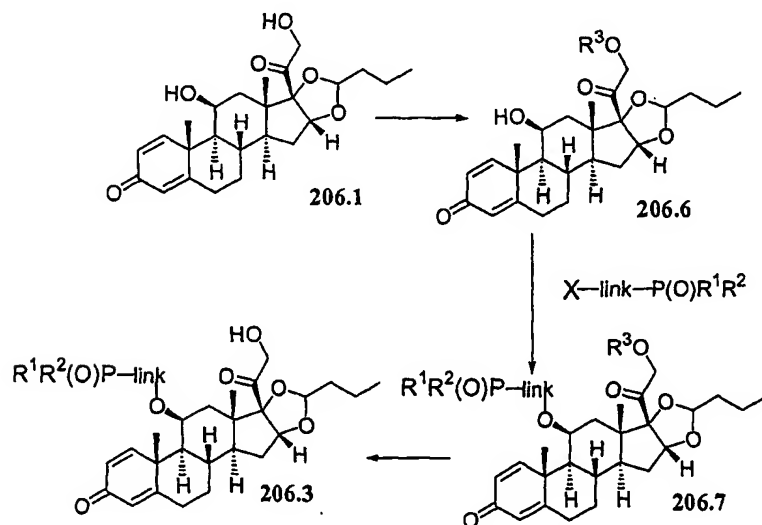
Representative compounds of the invention can be prepared as illustrated above. Derivatives of the C-21 primary hydroxy group are readily prepared by alkylating budesonide **205.1** with the appropriate phosphonate. A specific compound of the invention can be prepared as follows.



5 After chemoselective extraction of the primary hydroxy proton in **205.1** using one equivalent of sodium hydride, the phosphonate triflate is added to provide the ether **205.5**.

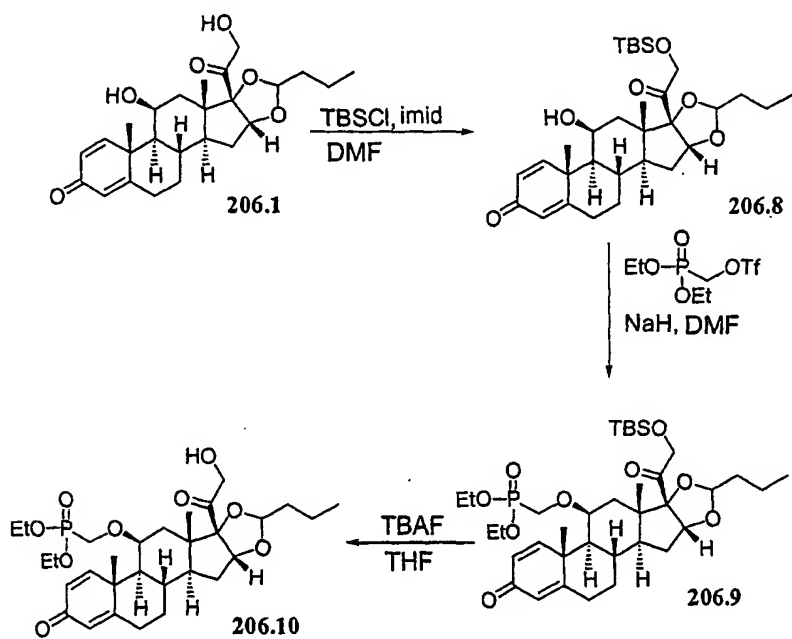
Example 206 Preparation of Representative Compounds of the Invention

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15 Representative compounds of the invention can be prepared as illustrated above. Again taking advantage of the reactivity difference between the primary and secondary hydroxy groups, the primary hydroxy group is masked by an appropriate protecting group. After alkylation at the secondary hydroxy moiety of **206.6** with a leaving group-attached phosphonate and subsequent

deprotection, desired analog **206.3** is obtained. A specific compound of the invention can be prepared as follows.

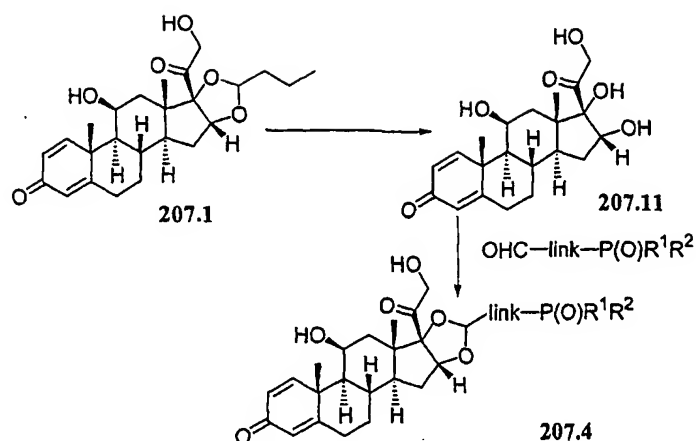


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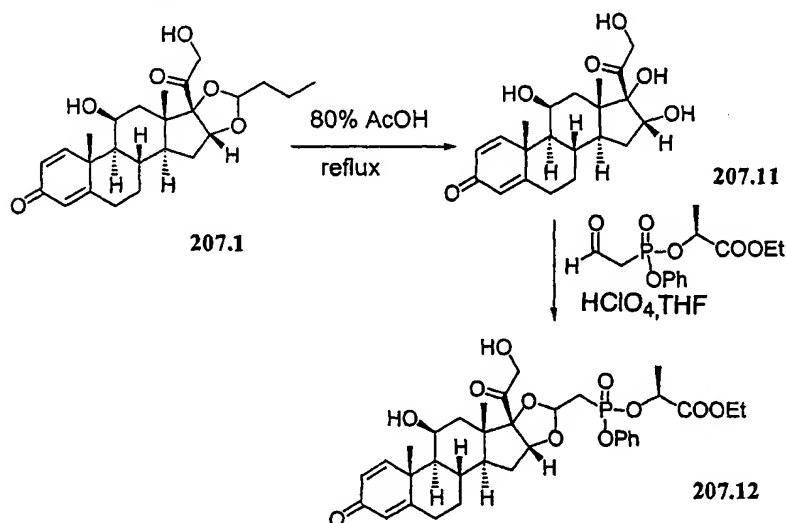
Budesonide **206.1** is chemoselectively protected as its silyl ether using the standard TBSCl and imidazole conditions. (*J. Am. Chem. Soc.* **1972**, *94*, 6190) Alkylation at the exposed secondary hydroxy group with sodium hydride and the phosphonate triflate furnishes the intermediate **206.9**. Final TBAF deprotection of the silyl ether affords the desired product **206.10**.

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Example 207 Preparation of Representative Compounds of the Invention

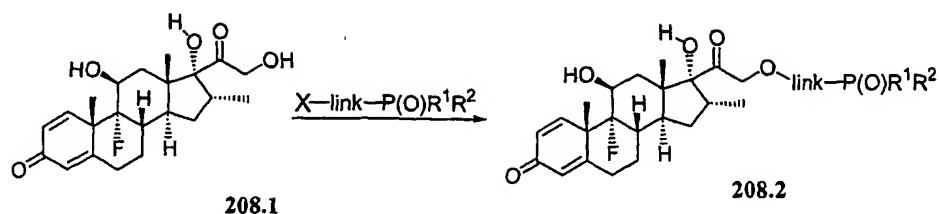


Representative compounds of the invention can be prepared as illustrated above. Phosphonate derivatives of the acetal are readily prepared from acidic hydrolysis of budesonide **207.1** to the diol **207.11**. Acetylation of the diol with a phosphonate aldehyde furnishes the desired acetal **207.4**. A specific compound of the invention can be prepared as follows.



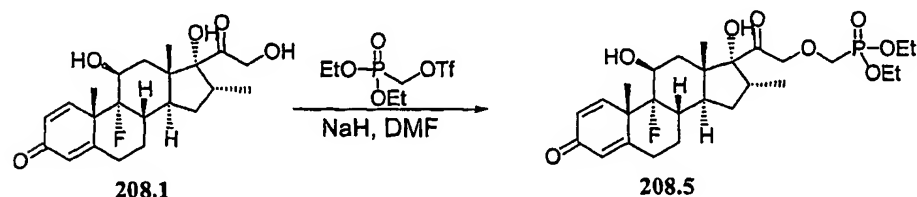
Budesonide **207.1** is first hydrolyzed in aqueous acetic acid. (*J. Am. Chem. Soc.* 1987, 109, 1565) The resulting diol **207.11** is acetalized with the phosphonate aldehyde and perchloric acid, affording the acetal **207.12**. (*J. Med. Chem.* 1996, 39, 4888-4896)

Example 208 Preparation of Representative Compounds of the Invention



Representative compounds of the invention can be prepared as illustrated above. Derivatization at the C-21 hydroxy group is accomplished through

5 alkylation of dexamethasone **208.1** with the appropriate phosphonate, furnishing analogs of formula **208.2**. A specific compound of the invention can be prepared as follows.

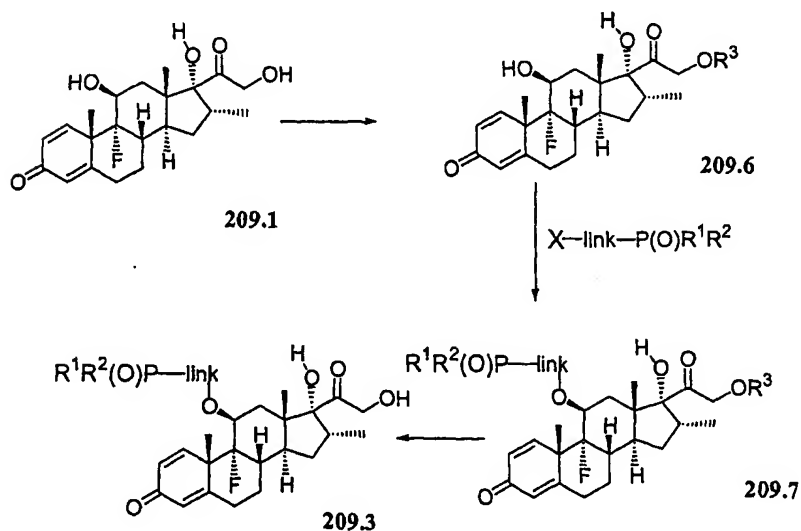


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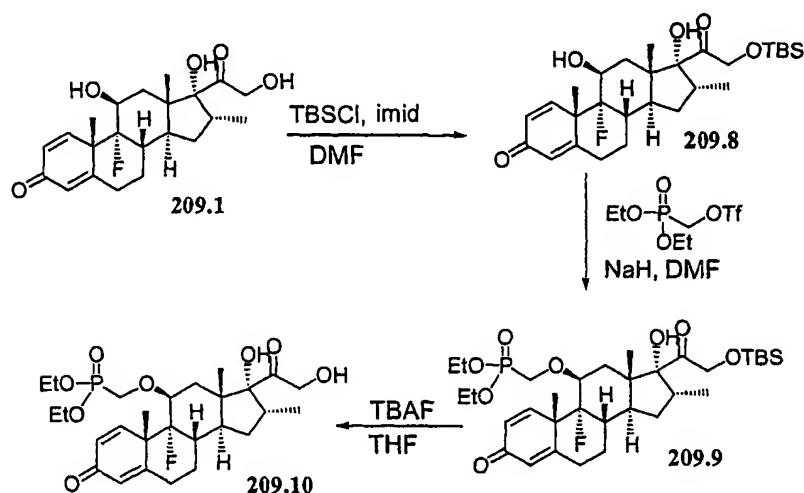
After sodium hydride extraction of the primary hydroxy proton in **208.1**, diethyl phosphonate triflate is added to afford ether **208.5**.

Example 209 Preparation of Representative Compounds of the Invention

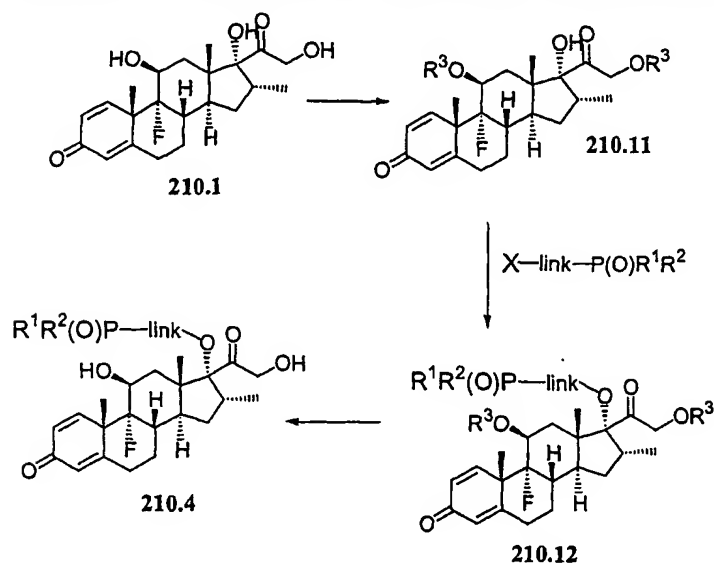
15



Representative compounds of the invention can be prepared as illustrated above. Phosphonate appendages linked to the C-11 hydroxy group can be attained by utilizing protecting groups on dexamethasone **209.1**. Following protection of the primary hydroxy group, protected intermediate **209.6** is alkylated at the more exposed C-11 hydroxy site. Final deprotection provides the desired product **209.3**. A specific compound of the invention can be prepared as follows.

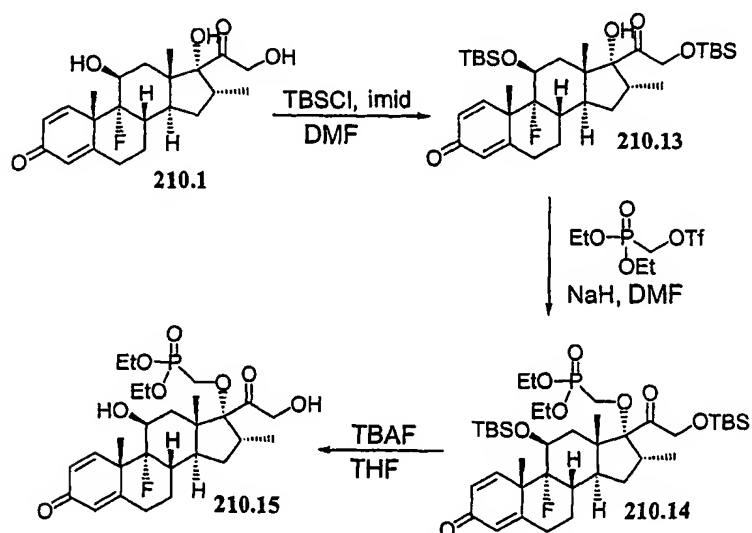


Dexamethasone **209.1** is protected as its silyl ether using the standard TBSCl and imidazole conditions (*J. Am. Chem. Soc.* 1972, 94, 6190). After alkylating with the diethyl phosphonate triflate, the resulting intermediate **209.9** is treated with TBAF to give the diol **209.10**.

Example 210 Preparation of Representative Compounds of the Invention

Representative compounds of the invention can be prepared as illustrated
 5 above. Protection of dexamethasone **210.1** at the two less hindered sites
 furnishes alcohol **210.11**, which is alkylated at the only exposed hydroxy group
 with the appropriate phosphonate. Removal of the protecting groups completes
 the construction of analog **210.4**. A specific compound of the invention can be
 prepared as follows.

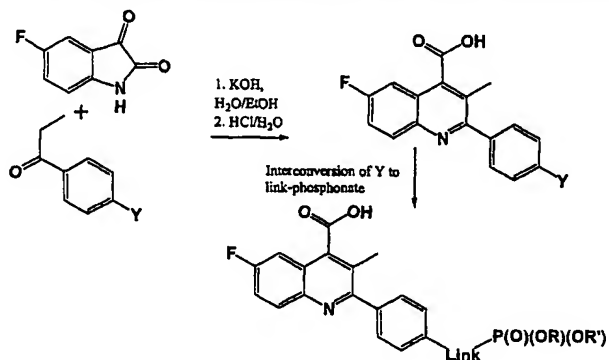
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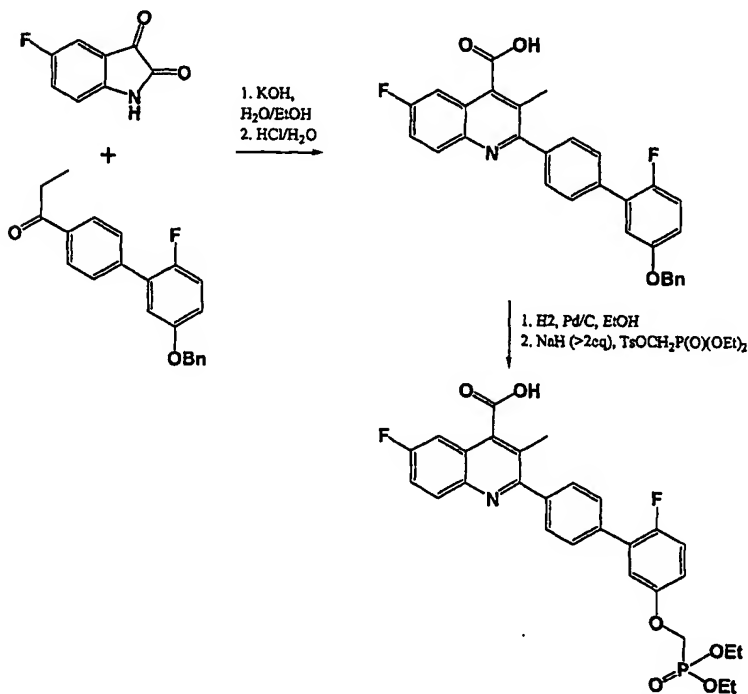
Again dexamethasone **210.1** is protected as its TBS ether; however, harsher conditions should allow for bis-protection. After alkylating with the diethyl phosphonate triflate, the resulting intermediate **210.14** is treated with TBAF to give the desired phosphonate **210.15**.

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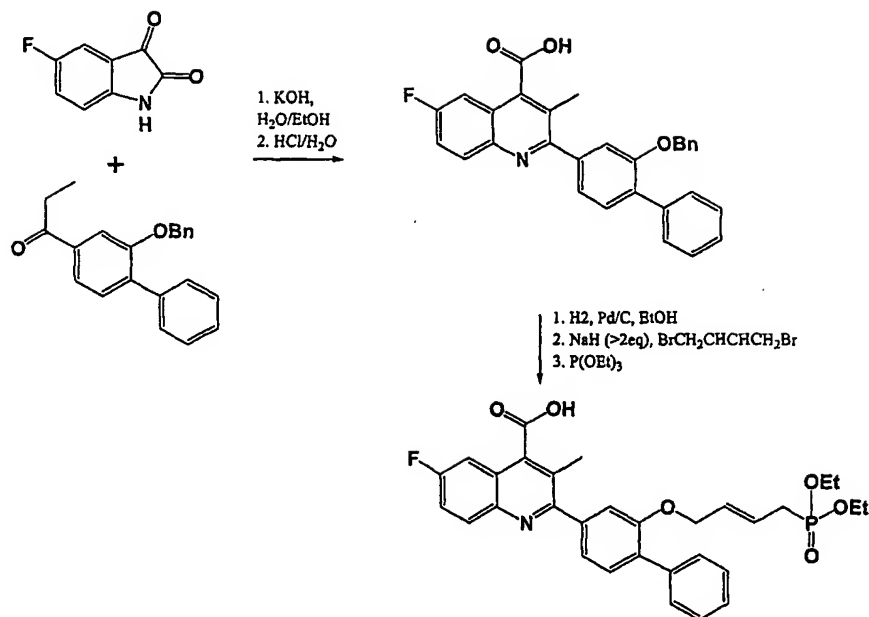
Example 211 Preparation of Representative Compounds of the Invention



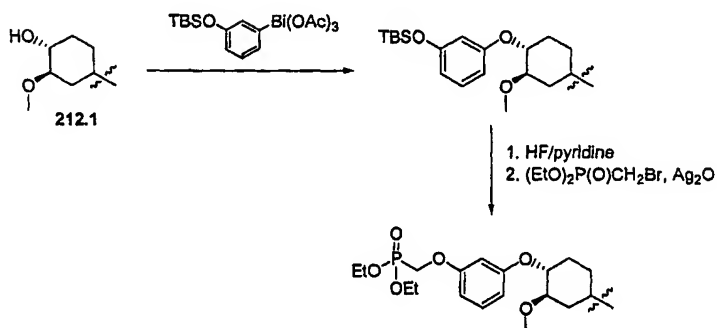
Representative compounds of the invention can be prepared as illustrated
 10 above. Specific compounds of the invention can be prepared as illustrated below.



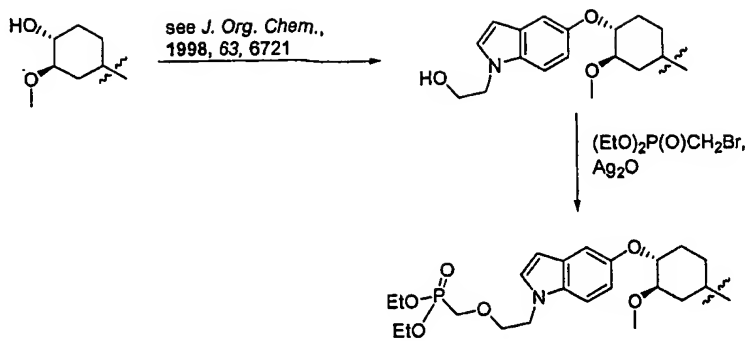
and



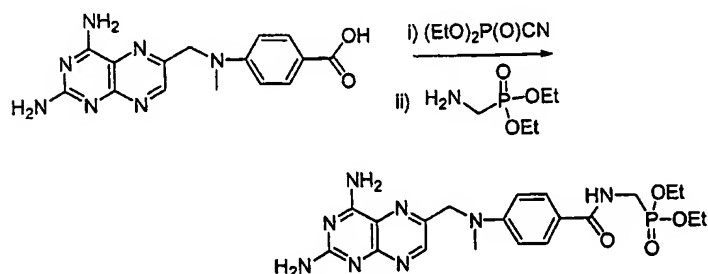
5 Example 212 Preparation of Representative Compounds of the Invention



Representative macrolide compounds of the invention, wherein the structure 212.1 is understood to be the compound tacrolimus, ascormycin or sirolimus, can be prepared as illustrated above, for example, using an aryl bismuth reagent such as that shown is described in *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 1035. Additionally, silver salts have been used to mediate alkylations on immunosuppressive macrolides such as these: see *J. Med. Chem.*, **1998**, *41*, 1764. Specific compounds of the invention can be prepared as illustrated below.



Example 213 Preparation of a Representative Compound of the Invention -
(2-{4-[(2,4-Diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-
methyl)-phosphonic acid diethyl ester

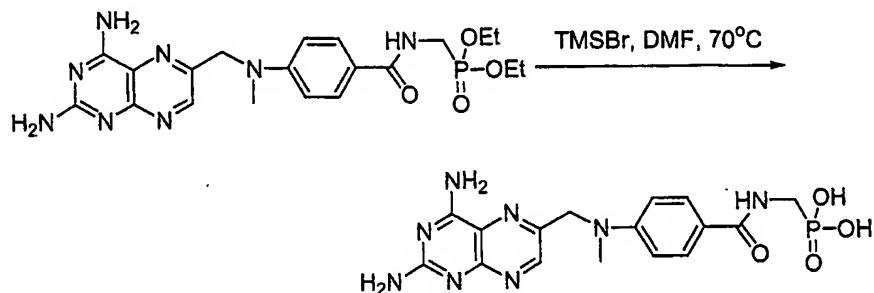


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To a solution of 4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoic acid hemihydrochloride dihydrate (67.0 mg, 177 μmol) in DMF (3.0 mL) was added diethyl cyanophosphonate (34.8 μL , 230 μmol) and diisopropylethylamine (Hunig's Base, DIEA, 30.4 μL , 177 μmol). The solution was stirred at ambient temperature for 4 hours when diethyl(aminomethyl)-phosphonate (45.4 mg, 177 μmol) was added. The solution was stirred for 4 additional hours, when complete consumption of the starting materials was observed. The reaction was worked up by removal of the solvent *in vacuo* and purifying the residue by silica gel chromatography using $\text{MeOH}-\text{CH}_2\text{Cl}_2$ (10-30%). The product collected from this chromatography step was sufficiently pure to be carried on to the next reaction. A small amount of the product (20 mg) was repurified by RP HPLC on C_{18} column using $\text{H}_2\text{O}/\text{acetonitrile}$ (2-95%) to provide 12.9 mg (76%) of the pure product. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.19 (t, 6H, $J=7.2$ Hz), 3.21 (s, 3H), 3.70 (m, 2H), 4.00 (q, 4H, $J=7.2$ Hz), 4.81 (s, 2H), 6.81 (d, 2H, $J=9$ Hz), 7.71 (d, 2H, $J=9$ Hz), 8.40 (br s, 1H), 8.61 (s, 1H). ^{31}P (121.4 MHz, $\text{DMSO}-d_6$) δ 23.4. MS (m/z) 475.2 $[\text{M}+\text{H}]^+$, 597.2 $[\text{M}+\text{Na}]^+$.

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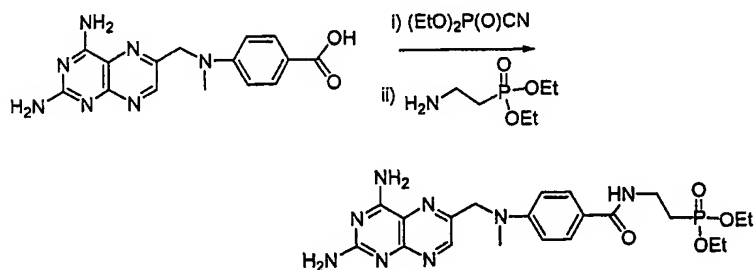
Example 214 Preparation of a Representative Compound of the Invention -
(2-{4-[(2,4-Diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-
methyl)-phosphonic acid



To a solution of crude (2-{4-[(2,4-Diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-ethyl)-phosphonic acid diethyl ester post silica column chromatography (60 mg, 126 μmol) in dry DMF (0.90 mL) was added trimethylsilyl bromide (bromotrimethylsilane, TMSBr, 130.6 μL , 1,010 μmol) at ambient temperature. The solution was then heated at 70 $^{\circ}\text{C}$ for 4.0 hours, after which the reaction mixture was allowed to cool to room temperature. The solvent volume was reduced to ~ 700 μL *in vacuo* and diluted with H_2O (100 μL). This solution was purified by RP HPLC on C_{18} column using H_2O /acetonitrile (2-95%) to provide 26.8 mg (51%) of the desired compound as a yellow solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 3.18 (s, 3H), 3.50 (m, 2H), 4.77 (s, 2H), 6.79 (d, 2H, $J=9$ Hz), 7.79 (d, 2H, $J=9$ Hz), 8.07 (br s, 1H), 8.56 (s, 1H); MS (m/z) 419.2 $[\text{M}+\text{H}]^+$.

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Example 215 Preparation of a Representative Compound of the Invention -
(2-{4-[(2,4-Diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-
ethyl)-phosphonic acid diethyl ester

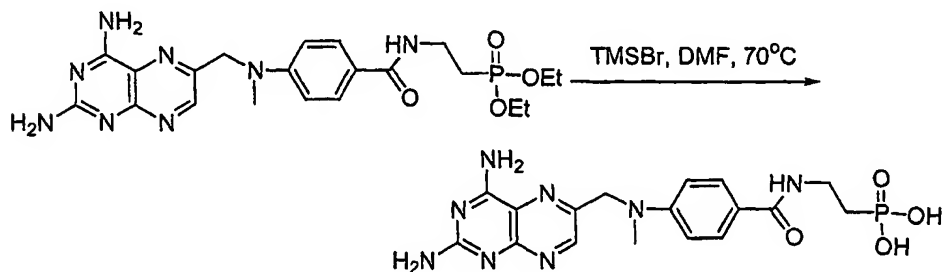


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To a solution of 4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoic acid hemihydrochloride dihydrate (61.2 mg, 161 μmol) in DMF (2.8 mL) were added diethyl cyanophosphonate (31.8 μL , 210 μmol) and DIEA (27.8 μL , 161 μmol). The solution was stirred at ambient temperature for 4 hours, when diethyl(aminoethyl)phosphonate (43.8 mg, 161 μmol) was added. The solution was stirred for 3 additional hours, by which time complete consumption of the starting materials was observed. The reaction was worked up by removal of the solvent *in vacuo* and purifying the residue by silica gel chromatography using $\text{MeOH}-\text{CH}_2\text{Cl}_2$ (10-30%). The product collected from this chromatography step was sufficiently pure to be carried on to the next reaction. A small amount of the product (32 mg) was re-purified by RP HPLC on C_{18} column using $\text{H}_2\text{O}/\text{acetonitrile}$ (2-95%) to provide 19 mg (70%) of the pure product. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.21 (t, 6H, $J=7$ Hz), 1.95- 2.05 (m, 2H), 3.20 (s, 3H), 3.13- 3.22 (m, 2H), 3.98 (appt septet, 4H, $J=7$ Hz), 4.79 (s, 2H), 6.80 (d, 2H, $J=9$ Hz), 7.65 (d, 2H, $J=9$ Hz), 8.20 (br s, 1H), 8.60 (s, 1H). ^{31}P (121.4 MHz, $\text{DMSO}-d_6$) δ 28.9. MS (m/z) 489.2 $[\text{M}+\text{H}]^+$, 511.2 $[\text{M}+\text{Na}]^+$.

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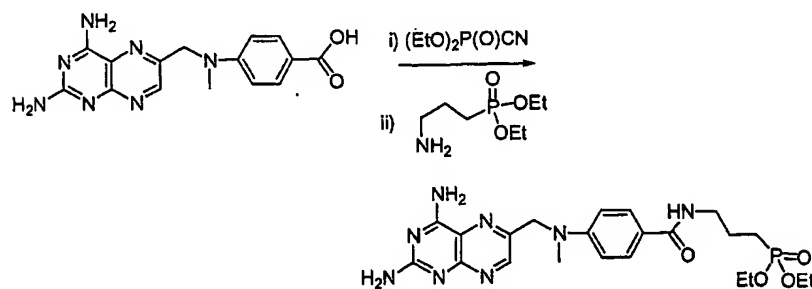
**Example 216 Preparation of a Representative Compound of the Invention -
(2-{4-[(2,4-Diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-ethyl)-phosphonic acid**



To a solution of crude (2-{4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-ethyl)-phosphonic acid diethyl ester post silica column chromatography (61 mg, 125 μ mol) in dry DMF (1.00 mL) was added TMSBr (129.0 μ L, 999.2 μ mol) at ambient temperature. The solution was then heated at 70 $^{\circ}$ C for 5.5 hours, when LCMS analysis demonstrated the reaction to be 90% complete. The reaction mixture was allowed to cool to room temperature and stirred for an additional 12 hours. The reaction was worked up by removal of the solvent *in vacuo* and dissolving the residue in DMF / H₂O (800 μ L, 1:1) and 1N aqueous NaOH (15 μ L). The product was purified by RP HPLC on C₁₈ column using H₂O/acetonitrile (2-95%) to provide 29 mg (53%) of the desired compound as a yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.67- 1.85 (m, 2H), 3.19 (s, 3H), 3.25- 3.40 (m, 2H), 4.76 (s, 2H), 6.71 (br s, 2H), 5.80 (d, 2H, *J*= 9 Hz), 7.64 (d, 2H, *J*= 9 Hz), 7.73 (br s, 2H), 8.15 (br s, 1H), 8.56 (s, 1H). ³¹P (121.4 MHz, DMSO-*d*₆) δ 23.0. MS (*m/z*) 431.3 [M-H]⁻.

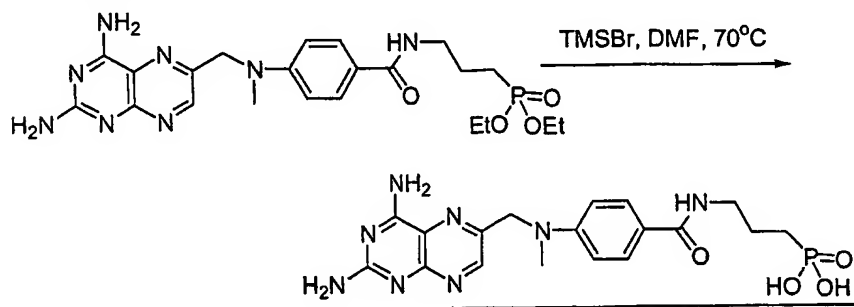
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**Example 217 Preparation of a Representative Compound of the Invention –
(2-{4-[(2,4-Diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-
propyl)-phosphonic acid diethyl ester**



- 5 To a solution of 4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoic acid hemihydrochloride dihydrate (61.2 mg, 161 μmol) in DMF (2.8 mL) were added diethyl cyanophosphonate (31.8 μL , 210 μmol) and DIEA (27.8 μL , 161 μmol). The solution was stirred at ambient temperature for 3 hours, when diethyl(aminopropyl)phosphonate (34.9 mg, 122.6 μmol) was added. The
- 10 solution was stirred for 2 additional hours, whereupon complete consumption of the starting materials was observed. The reaction was worked up by removal of the solvent *in vacuo* and purifying the residue by silica gel chromatography using MeOH-CH₂Cl₂ (10-30%). The product (65.5 mg) collected from this chromatography step was sufficiently pure to be carried on to the next reaction.
- 15 A small amount (32.8 mg) was re-purified by RP HPLC on C₁₈ column using H₂O/acetonitrile (2-95%) to provide 23.2 mg (75%) of the pure product. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.20 (t, 6H, *J* = 7.2 Hz), 1.64- 1.75 (m, 4H), 3.22 (s, 3H), 3.41 (m, 2H), 3.98 (appt septet, 4H, *J* = 7.2 Hz), 4.85 (s, 2H), 6.79 (d, 2H, *J* = 9 Hz), 7.68 (d, 2H, *J* = 9 Hz), 8.17 (br s, 1H), 8.70 (s, 1H); ³¹P (121.4
- 20 MHz, DMSO-*d*₆) δ 31.9; MS (*m/z*) 503.2 [M+H]⁺.

**Example 218 Preparation of a Representative Compound of the Invention –
(2-{4-[(2,4-Diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-
propyl)-phosphonic acid**



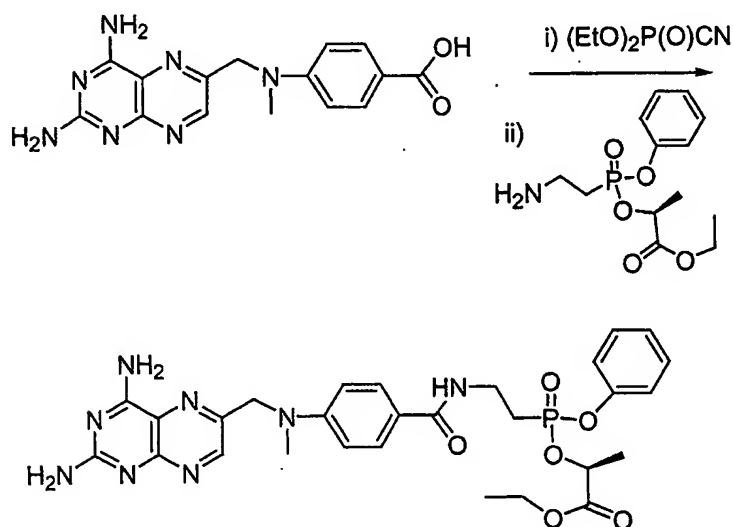
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To a solution of crude (2-{4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-propyl)-phosphonic acid diethyl ester post silica column chromatography (32.2 mg, 66.2 μmol) in dry DMF (0.50 mL) was added TMSBr (68.0 μL , 529.6 μmol) at ambient temperature. The solution was then heated at

10 70 °C for 1.0 hour, when LCMS analysis demonstrated the reaction to be complete. The reaction mixture was allowed to cool to room temperature, and water (60 μL) and methanol (60 μL) were added. The crude reaction mixture was purified by RP HPLC on C₁₈ column using H₂O/acetonitrile (2-95%) to provide 11.2 mg (38%) of the desired compound as a yellow solid. ¹H NMR

15 (300 MHz, DMSO-*d*₆) δ 1.50 (m, 2H), 1.61 (m, 2H), 3.22 (s, 3H), 3.25- 3.40 (m, 2H), 4.84 (s, 2H), 6.80 (d, 2H, *J* = 9 Hz), 7.69 (d, 2H, *J* = 9 Hz), 8.20 (br s, 1H), 8.69 (s, 1H). ³¹P (121.4 MHz, DMSO-*d*₆) δ 26.3. MS (*m/z*) 447.3 [M-H]⁻.

Example 219 Preparation of a Representative Compound of the Invention –
2-[(2-{4-[(2,4-diaminopteridin-6-ylmethyl)methylamino]benzoylamino}-
ethyl)phenoxyphosphinoyloxy]propionic acid ethyl ester [diastereomeric
mixture at phosphorus]



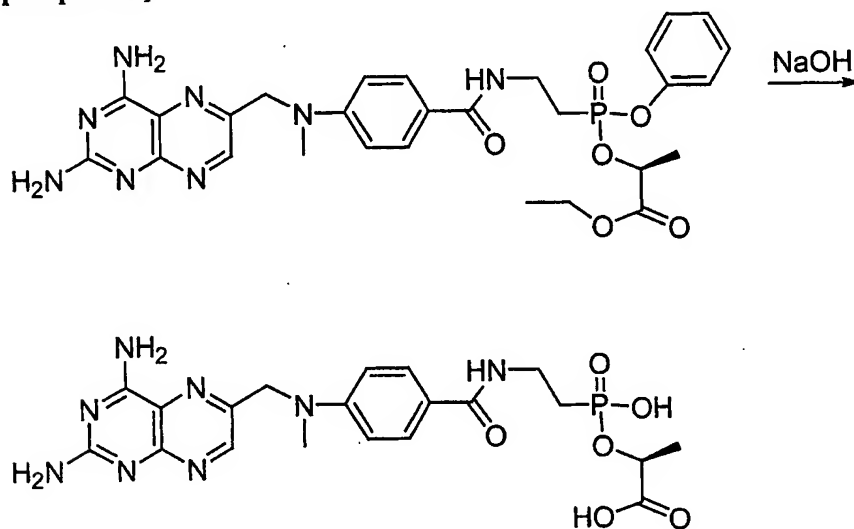
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To a solution of 4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoic acid hemihydrochloride dihydrate (60.0 mg, 158.3 μmol) in DMF (2.5 mL) were added diethyl cyanophosphonate (31.2 μL , 205.7 μmol) and DIEA
 10 (81.8 μL , 474.9 μmol). The solution was stirred at ambient temperature for 3.5 hours, when a solution of (S)-2-[(2-aminoethyl)phenoxyphosphinoyloxy]-propionic acid ethyl ester mono acetic acid salt (57.1 mg, 158.3 μmol ; mixture of diastereomers at phosphorus) in DMF (200 μL) was added. The solution was stirred for 1.5 additional hours, whereupon complete consumption of the starting
 15 materials was observed. The solvent was removed *in vacuo* and the crude material was purified by silica gel chromatography using MeOH-CH₂Cl₂ (10-30%). A small amount of the product (24.8 mg) was repurified by RP HPLC on C₁₈ column using H₂O/acetonitrile (2-95%) to provide 15.8 mg (65%) of the pure product. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.17 – 1.27 (m, 3H), 1.32 (d,
 20 2H, J = 7.5 Hz), 1.42 (d, 1H, J = 7.5 Hz) 2.27 (m, 2H), 3.19 (s, 3H), 3.53 (m, 2H), 4.08 – 4.14 (m, 2H), 4.77 (s, 2H), 4.98 (m, 1H), 6.72 (br s, 1H), 6.81 (d,

2H, $J = 9$ Hz), 7.21 (m, 3H), 7.36 (m, 2H), 7.66 (d, 2H, $J = 9$ Hz), 8.26 (br s, 1H), 8.56 (s, 1H); ^{31}P (121.4 MHz, DMSO- d_6) δ 26.6, 27.4. MS (m/z) 609.2 $[\text{M}+\text{H}]^+$.

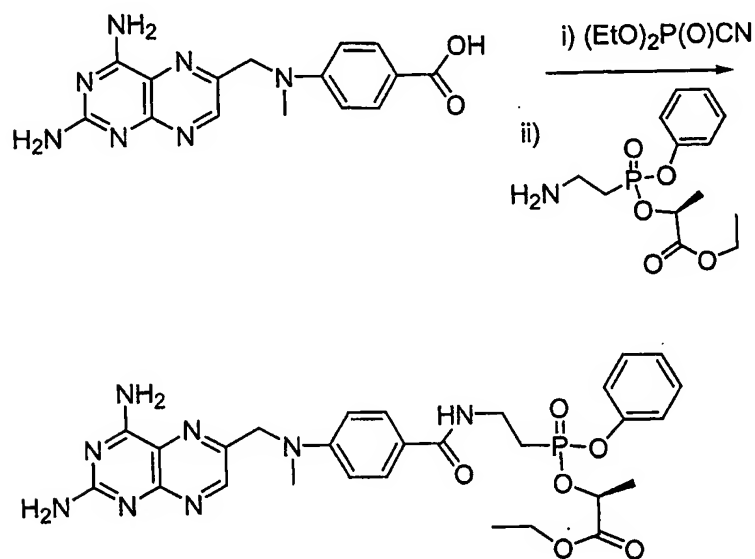
Example 220 Preparation of a Representative Compound of the Invention –

- 5 **2-[(2-{4-[(2,4-diaminopteridin-6-ylmethyl)methylamino]benzoylamino}ethyl)phenoxyphosphinoyloxy]-propionic acid [diastereomeric mixture at phosphorus]**



- 10 To a solution of 2-[(2-{4-[(2,4-diaminopteridin-6-ylmethyl)amino]benzoylamino}ethyl)phenoxy-phosphinoyloxy]propionic acid ethyl ester (mixture of diastereomers at phosphorus; 40.0 mg, 65.7 μmol) in DMF (0.4 mL), acetonitrile (0.2 mL) and water (0.2 mL) was added aqueous sodium hydroxide (1 N, 131.4 μL). The solution was stirred at ambient temperature for 4 hours.
- 15 The solvents were removed *in vacuo* and the crude product was purified by RP HPLC on C_{18} column using H_2O /acetonitrile (2-95%) to provide 23.7 mg (71.3%) of the pure product. ^1H NMR (300 MHz, DMSO- d_6) δ 1.30 (d, 2H, $J = 6.9$ Hz), 1.79 (m, 2H), 3.21 (s, 3H), 3.37 (m, 2H), 4.61 (m, 1H), 4.81 (s, 2H), 6.79 (d, 2H, $J = 8.7$ Hz), 7.64 (d, 2H, $J = 9.7$ Hz), 8.25 (br s, 1H), 8.63 (s, 1H);
- 20 ^{31}P (121.4 MHz, DMSO- d_6) δ 25.1. MS (m/z) 505.2 $[\text{M}+\text{H}]^+$.

Example 221 Preparation of a Representative Compound of the Invention –
2-[(2-{4-[(2,4-diaminopteridin-6-ylmethyl)methylamino]benzoyl-
amino}ethyl)phenoxyphosphinoyloxy]propionic acid ethyl ester
[diastereomerically pure at phosphorus]

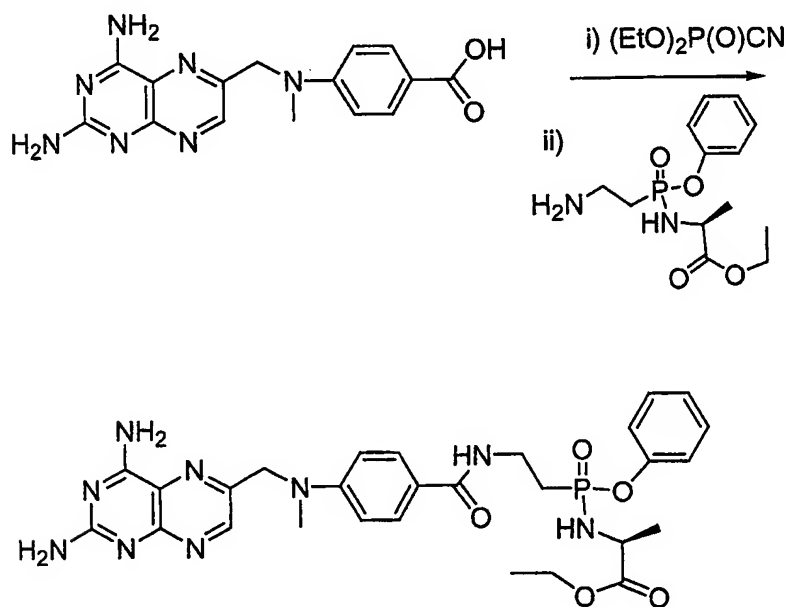


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To a solution of 4-[(2,4-diaminopteridin-6-ylmethyl)-methyl-
 amino]benzoic acid hemihydrochloride dihydrate (101.9 mg, 268.9 μmol) in
 DMF (3.3 mL) were added diethyl cyanophosphonate (53.0 μL , 349.5 μmol) and
 10 DIEA (138.0 μL , 806.7 μmol). The solution was stirred at ambient temperature
 for 2.5 hours, whereupon (S)-2-[(2-aminoethyl)phenoxyphosphinoyloxy]-
 propionic acid ethyl ester mono acetic acid salt (diastereomerically pure at
 phosphorus; 268.9 μmol) in DMF (500 μL) was added. The solution was stirred
 for 30 additional minutes, whereupon complete consumption of the starting
 15 materials was observed. The solvent was removed *in vacuo* and the crude
 material was purified by silica gel chromatography using MeOH-CH₂Cl₂ (10-
 30%). A small amount of the product (40.0 mg) was repurified by RP HPLC on
 C₁₈ column using H₂O/acetonitrile (2-95%) to provide 28.7 mg (75.1%) of the
 pure product. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.15 (t, 3H, J = 7.2 Hz), 1.44
 20 (d, 3H, J = 6.9 Hz), 2.26 (m, 2H), 3.23 (s, 3H), 3.51 (m, 2H), 4.09 (q, 2H, J = 7.2

Hz), 4.86 (s, 2H), 5.01 (m, 1H), 6.81 (d, 2H, $J = 9.3$ Hz), 7.21 (m, 3H), 7.35 (m, 2H), 7.68 (d, 2H, $J = 9.3$ Hz), 8.29 (br s, 1H), 8.71 (s, 1H); ^{31}P (121.4 MHz, DMSO- d_6) δ 26.6. MS (m/z) 609.2 $[\text{M}+\text{H}]^+$.

5 **Example 222 Preparation of a Representative Compound of the Invention – 2-[(2-{4-[(2,4-diaminopteridin-6-ylmethyl)methylamino]benzoylamino}-ethyl)-phenoxyphosphinoylamino]propionic acid ethyl ester (mixture of diastereomers at phosphorus)**



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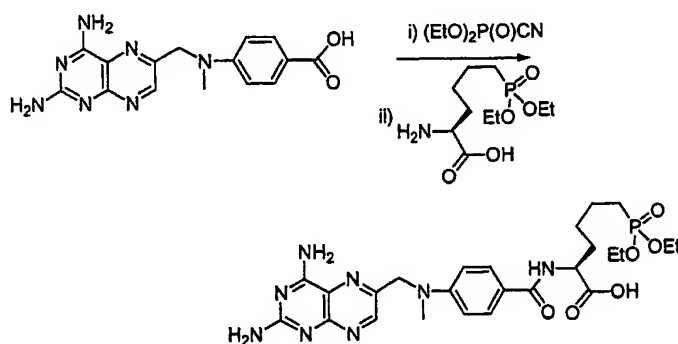
To a solution of 4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoic acid hemihydrochloride dihydrate (39.6 mg, 104.0 μmol) in DMF (1.2 mL) were added diethyl cyanophosphonate (20.6 μL , 136.1 μmol) and DIEA (36.0 μL , 209.4 μmol). The solution was stirred at ambient temperature for 3 hours, when (S)-2-[(2-aminoethyl)phenoxyphosphinoylamino]propionic acid ethyl ester mono acetic acid salt (mixture of diastereomers at phosphorus; 104.0 μmol) in DMF (200 μL) was added. The solution was stirred for 30 minutes when complete consumption of the starting materials was observed. An aliquot (66%) of the reaction was purified by silica gel chromatography using MeOH-

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CH₂Cl₂ (10-30%), yielding 27.2 mg of crude product. A small amount of the product (10 mg) was repurified by RP HPLC on C₁₈ column using H₂O/acetonitrile (2-95%) to provide 4.2 mg (26%) of the pure product. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.11 (t, 3H, *J* = 6.9 Hz), 1.18 (d, 3H, *J* = 7.2 Hz), 2.06-2.17 (m, 2H), 3.20 (s, 3H), 3.51 (m, 2H), 3.88 (m, 1H), 4.02 (m, 2H), 4.79 (s, 2H), 5.61 (m, 1H), 6.80 (d, 2H, *J* = 9 Hz), 6.98 (br s, 1H), 7.18 (m, 3H), 7.32 (m, 2H), 7.67 (d, 2H, *J* = 9 Hz), 8.20 (br s, 1H), 8.59 (s, 1H) ³¹P (121.4 MHz, DMSO-*d*₆) δ 29.5, 30.1. MS (*m/z*) 608.2 [M+H]⁺.

10 **Example 223 Preparation of a Representative Compound of the Invention – 2-{4-[(2,4-Diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-6-(diethoxy-phosphoryl)-hexanoic acid**



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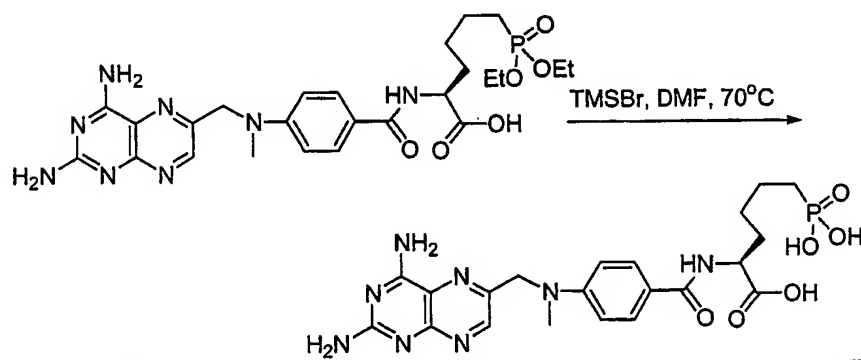
To a solution of 4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoic acid hemihydrochloride dihydrate (63.0 mg, 166.2 μmol) in DMF (2.8 mL) were added diethyl cyano phosphonate (30.8 μL, 199.4 μmol) and DIEA (85.8 μL, 498.6 μmol). The solution was stirred at ambient temperature for 3.5 hours when (L)-2-amino-6-diethylphosphonohexanoic acid (44.3 mg, 166.2 μmol) was added. The solution was stirred for 48 additional hours. The reaction was worked up by removal of the solvent *in vacuo* and purifying the residue by silica gel chromatography using MeOH-CH₂Cl₂ (10-30%). The product (87 mg) collected from this chromatography step was sufficiently pure to be carried on to the next reaction. An aliquot of the product (51.0 mg) was repurified by RP HPLC on C₁₈ column using H₂O/acetonitrile (2-95%) to provide 24.7 mg (44%)

of the pure product. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.18 (t, 6H, $J = 6.9$ Hz), 1.42 (m, 4H), 1.65 (m, 4H), 3.20 (s, 3H), 3.92 (m, 4H), 4.29 (m, 1H), 4.78 (s, 2H), 6.72 (br s, 1H), 6.81 (d, 2H, $J = 9$ Hz), 7.73 (d, 2H, $J = 9$ Hz), 8.14 (d, 1H, $J = 7.8$ Hz), 8.56 (s, 1H); ^{31}P (121.4 MHz, $\text{DMSO}-d_6$) δ 31.8; MS (m/z) 574.3

5 $[\text{M}]^+$.

Example 224 Preparation of a Representative Compound of the Invention –
2-{4-[(2,4-Diaminopteridin-6-ylmethyl)methylamino]benzoylamino}-6-
(phosphoryl)hexanoic acid

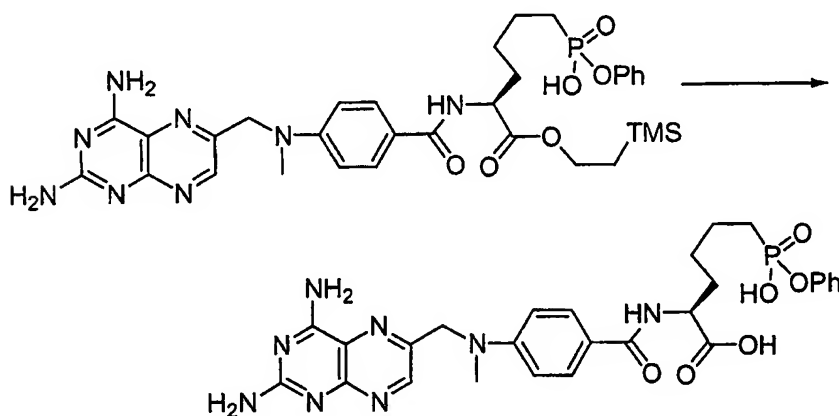
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To a solution of crude 2-{4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-
 amino]-benzoylamino}-2'-(L)-(6'-(phosphonic acid diethyl ester) hexanoic
 15 acid) post silica column chromatography (20 mg, 34.6 μmol) in dry DMF (0.60
 mL) was added TMSBr (18.0 μL , 139.2 μmol) at ambient temperature. The
 solution was then heated at 70 °C for 18 hours, after which the reaction mixture
 was allowed to cool to room temperature. The solvent was removed *in vacuo* and
 dissolved in DMF (400 μL) and water (60 μL). This solution was purified by RP
 20 HPLC on C_{18} column using H_2O /acetonitrile (2-95%) to provide 8.9 mg (49%)
 of the product as a yellow solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.45 (m,
 6H), 1.75 (m, 2H), 3.20 (s, 3H), 4.25 (m, 1H), 4.77 (s, 2H), 6.62 (br s, 1H), 6.80
 (d, 2H, $J = 8.7$ Hz), 7.73 (d, 2H, $J = 8.7$ Hz), 8.14 (br s, 1H), 8.55 (s, 1H); MS
 (m/z) 519.2 $[\text{M}+\text{H}]^+$.

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Example 225 Preparation of a Representative Compound of the Invention –
2-{4-[(2,4-Diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-6'-
(mono phenyl-phosphonate)hexanoic acid



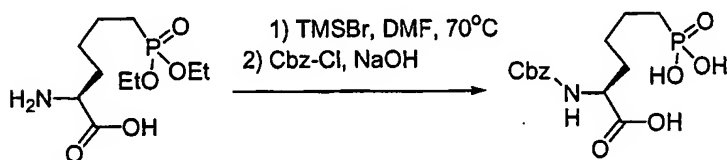
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The ethyl-TMS ester is hydrolyzed under suitable conditions to provide the corresponding acid of the invention.

The intermediate 2-{4-[(2,4-Diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-6'-(mono phenyl-phosphonate)-hexanoic acid TMS ethanol ester can be prepared as follows.

10

a. (L)-2- Cbz-Amino-hexanoic acid –6-phosphonic acid.



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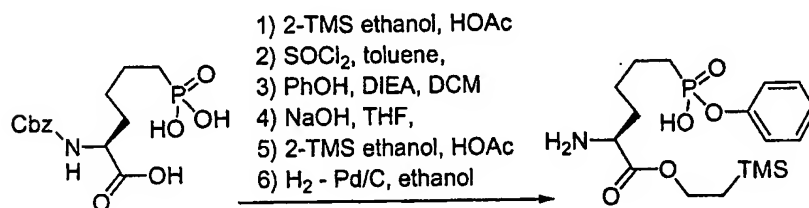
To a suspension of (L)-2-amino-6-(diethoxyphosphonyl)hexanoic acid (106 mg, 396.8 μmol) in dry DMF (2.00 mL) was added TMSBr (307.0 μL , 2,381.0 μmol) at ambient temperature. The solution was then heated at 70 $^{\circ}\text{C}$ for 2 hours, after which the reaction mixture was allowed to cool to room temperature. The solvent was removed *in vacuo*. The crude material was dissolved in water (0.25 mL) and NaOH (1-N, 2.50 mL). Benzyl chloroformate

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(79.3 μ L, 555.5 μ mol) was added and stirring at room temperature was continued. After 2 hours, the solution was washed with ether (2 mL) and the aqueous layer was acidified with aqueous HCl to pH 1. The aqueous layer was extracted with EtOAc (3x 5 mL). The combined organic extracts were dried over sodium sulfate. Filtration and evaporation of solvents yielded a crude product, which was sufficiently pure for further transformations. ^1H NMR (300 MHz, DMSO- d_6) δ 1.42 – 1.65 (m, 8H), 3.90 (m, 1H), 5.02 (s, 2H), 7.32 (s, 5H), 7.55 (m, 1H), 7.94 (s, 1H); ^{31}P (121.4 MHz, DMSO- d_6) δ 26.5; MS (m/z) 345.6 $[\text{M}+\text{H}]^+$.

10

b. (L)-2--Amino-hexanoic acid 2' TMS ethyl ester-6-phosphonic acid mono phenyl ester



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To a solution of (L)-2-Cbz-amino-hexanoic acid-6-phosphonic acid (137.3 mg, 397.9 μ mol) in 2-TMS ethanol (2.5 mL) was added acetyl chloride (50 μ L). Stirring at room temperature was continued. After 22 hours complete conversion was observed. The solvents were removed *in vacuo*. The crude material was sufficiently pure for the next step.

One half of the crude material (198.9 μ mol) was dissolved in toluene (3.0 mL) at room temperature. Thionyl chloride (167.2 mg, 1,416.0 μ mol) was added and the reaction mixture was heated at 70 $^{\circ}\text{C}$ (oil bath). After 4 hours, the reaction was cooled to room temperature and the solvent was removed *in vacuo*. The crude material was re-dissolved in methylene chloride (2.0 mL) and a solution of phenol (36.6 mg, 389.0 μ mol) and DIEA (67.0 μ L, 389.0 μ mol) in

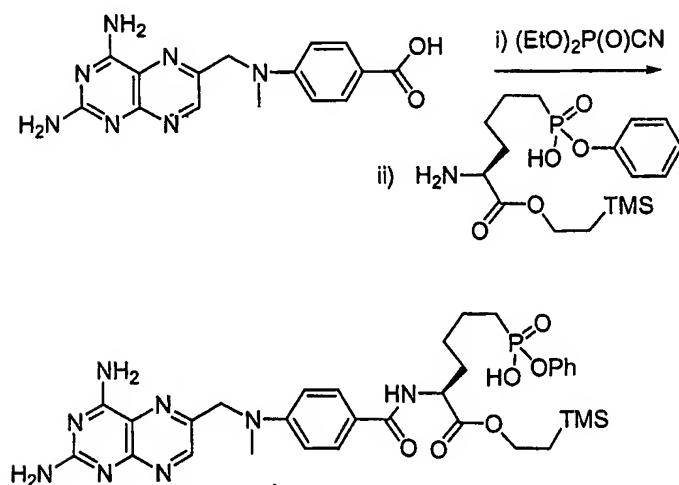
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methylene chloride (1.0 mL) was added. Stirring at room temperature was continued. After 4 hrs the solvents were removed *in vacuo*.

The crude material was dissolved in tetrahydrofuran (THF) (3.0 mL) and aqueous sodium hydroxide solution (1N, 0.885 mL) was added. Stirring at room temperature was continued. After 14 hours the solvent was removed *in vacuo* to provide the crude phosphonate mono phenyl ester (63.8 mg). This material was dissolved in 2-TMS ethanol (1.0 mL) and acetyl chloride (20 μ L) was added. Stirring at room temperature was continued. After 22 hours complete conversion to the carboxylate ester was observed. The solvents were removed *in vacuo*. The material was sufficiently pure for the next step.

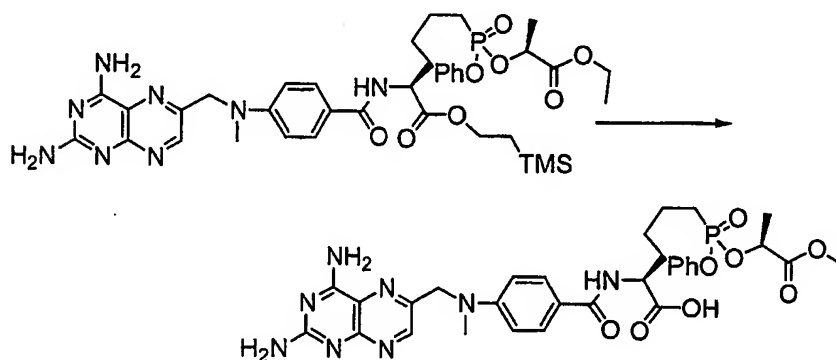
One half of the crude material (75 μ mol) was dissolved in ethanol (1.5 mL). Pd/C (5%, 20 mg) was added and the reaction was placed under an atmosphere of hydrogen gas. After 1.5 hours Celite was added and the crude reaction mixture was filtered through Celite. The solvents were removed *in vacuo* and the crude material was used in the next step without further purification.

c. 2-{4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-6'-(mono phenyl-phosphonate)-hexanoic acid TMS ethanol ester



To a solution of 4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoic acid hemihydrochloride dihydrate (22.7 mg, 60.0 μ mol) in DMF (0.80 mL) were added diethyl cyano phosphonate (12.4 μ L, 78.0 μ mol) and DIEA (31.0 μ L, 180.0 μ mol). The solution was stirred at ambient temperature for one hour when (L)-2-amino-6-monophenoxyposphonatohexanoic acid 2' TMS ethyl ester (70.5 μ mol), suspended in DMF (0.2 mL), was added. The solution was stirred for 3.5 additional hours. The crude reaction mixture was purified by RP HPLC on C₁₈ column using H₂O/acetonitrile (5-95%) to provide 19.4 mg (46%) of 2-{4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-6'-(mono phenyl-phosphonate)-hexanoic acid TMS ethanol ester. ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.0 (s, 9H), 0.91 (t, 2H, *J* = 8.1 Hz), 1.42 – 1.53 (m, 4H), 1.67 – 1.76 (m, 4H), 3.24 (s, 3H), 4.10 (t, 2H, *J* = 8.1 Hz), 4.29 (m, 1H), 4.86 (s, 2H), 6.81 (d, 2H, *J* = 9 Hz), 7.12 (m, 3H), 7.31 (m, 2H), 7.74 (d, 2H, *J* = 9 Hz), 8.14 (d, 1H, *J* = 7.8 Hz), 8.71 (s, 1H); ³¹P (121.4 MHz, DMSO-*d*₆) δ 26.2; MS (*m/z*) 695.2 [M]⁺.

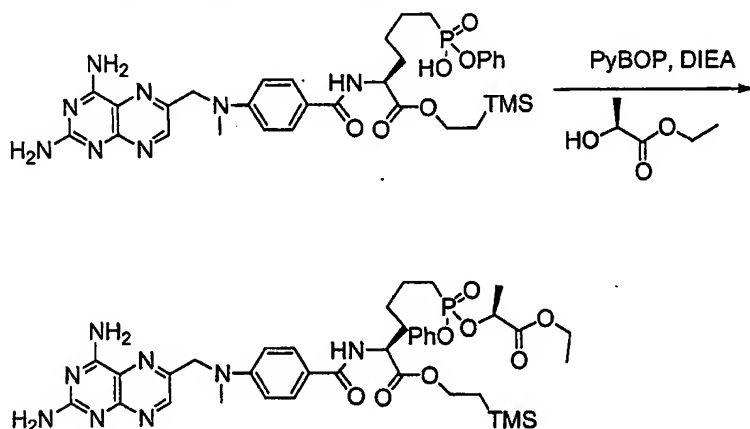
Example 226 Preparation of Representative Compounds of the Invention – 2-{4-[(2,4-Diamino-pteridin-6-ylmethyl)methylamino]benzoylamino}-6'-(mono phenyl mono (S) ethyl lactate-phosphonate)hexanoic acid



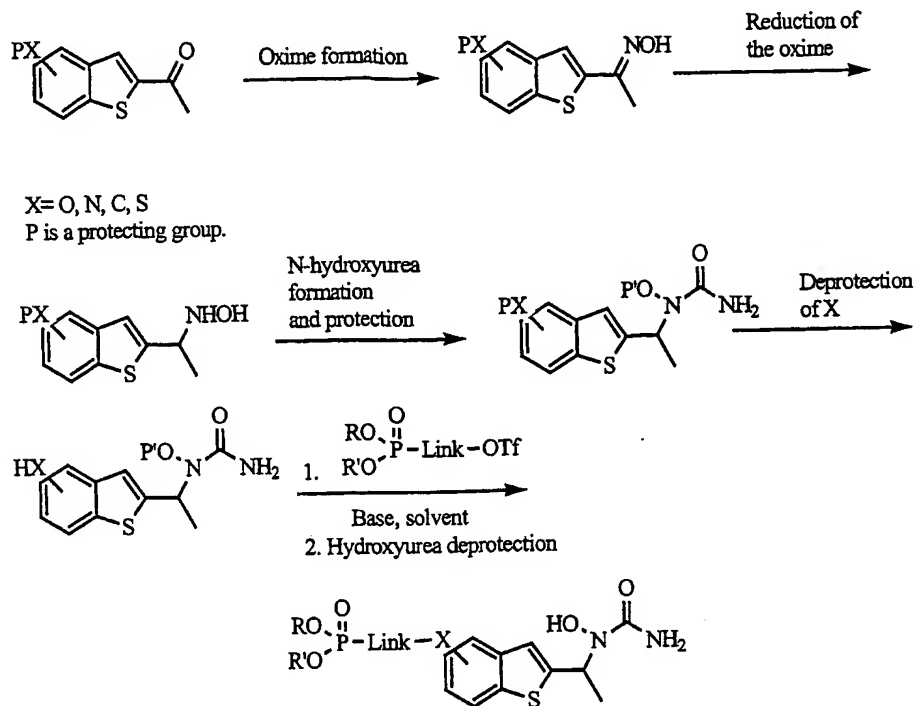
The ethyl-TMS ester is hydrolyzed under suitable conditions to provide the corresponding acid of the invention.

The intermediate 2-{4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-6'-(mono phenyl mono (S) ethyl lactate-phosphonate)-hexanoic acid TMS ethanol ester can be prepared as follows.

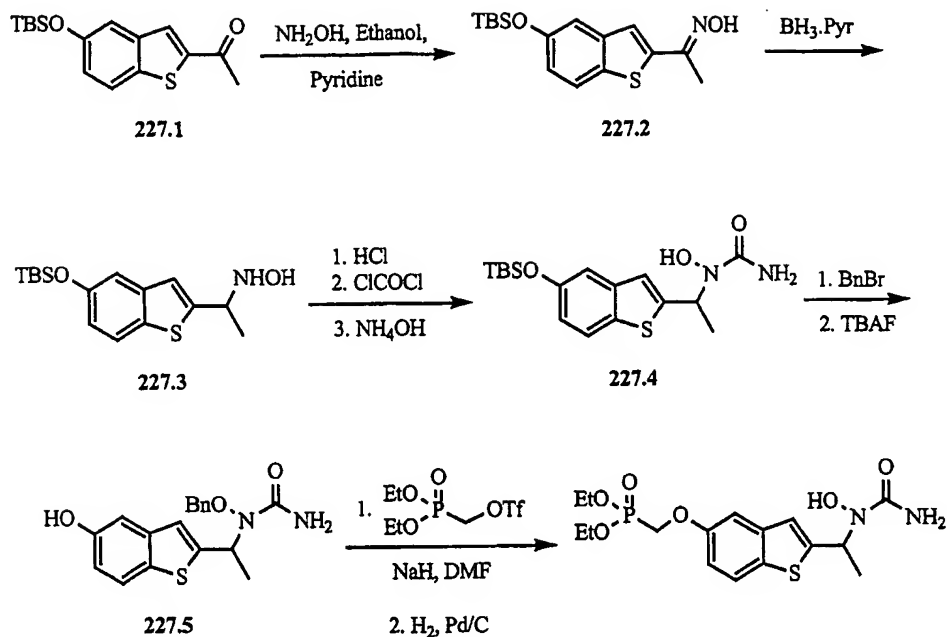
- 5 a. 2-{4-[(2,4-Diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-6'-(mono phenyl mono (S) ethyl lactate-phosphonate)-hexanoic acid TMS ethanol ester



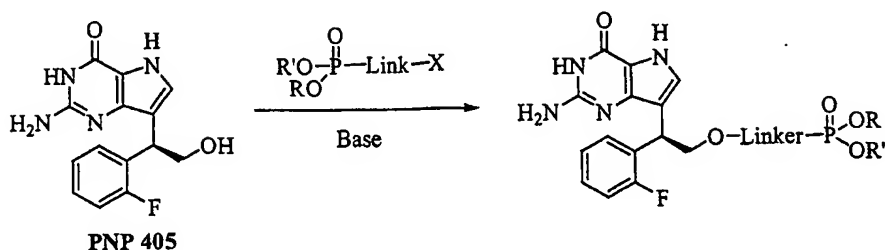
- 10 To a solution of 2-{4-[(2,4-diamino-pteridin-6-ylmethyl)-methyl-amino]-benzoylamino}-6'-(mono phenyl-phosphonate)-hexanoic acid TMS ethanol ester (14.5 mg, 20.8 μ mol, Example 225) in DMF (0.70 mL) was added PyBOP (32.4 mg, 62.4 μ mol), DIEA (21.4 mg, 166.4 μ mol) and (S) ethyl lactate (19.6 mg, 166.4 μ mol). The reaction mixture was stirred at room temperature for one hour.
- 15 The crude reaction mixture was purified by RP HPLC on C₁₈ column using H₂O/acetonitrile (5-95%) to provide 13.5 mg (81%) of the pure product as a mixture of diastereomers at phosphorus (~ 4:1). ¹H NMR (300 MHz, CDCl₃) δ 0.0 (s, 9H), 1.02 (t, 2H, *J* = 8.7 Hz), 1.23 (t, 3H, *J* = 9.3 Hz), 1.35 (d, 2.4H, *J* = 6.6 Hz), 1.42 – 1.53 (m, 4.6H), 1.67 – 1.86 (m, 4H), 3.14 (s, 3H), 4.03 – 4.27 (m, 4H), 4.71 (br s, 3H), 4.98 (m, 0.8H), 5.10 (m, 0.2H), 6.57 (d, 2H, *J* = 7.5 Hz), 7.00 (m, 1H), 7.16 (m, 3H), 7.30 (m, 2H), 7.63 (d, 2H, *J* = 7.5 Hz), 8.43 (s, 1H);
- 20 ³¹P (121.4 MHz, DMSO-*d*₆) δ 30.5, 29.2; MS (*m/z*) 795.2 [M]⁺.

Example 227 Preparation of a Representative Compound of the Invention

- 5 Representative compounds of the invention can be prepared as illustrated above. A specific compound of the invention can be prepared as follows.

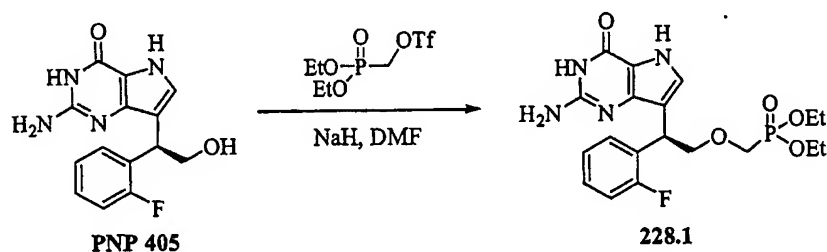


1-(5-Hydroxy-benzo[b]thiophen-2-yl)-ethanone (prepared as described in Krubsack, A. J. *et al.*, *J. Org. Chem.*, **1975**, *40*, 3179) is protected using a TBS group as described in Greene, T., *Protective groups in organic synthesis*, Wiley-Interscience, 1999 to provide compound **227.1** (in which X= O and P= TBS). Treatment of compound **227.1** with hydroxylamine in ethanol/pyridine provides oxime **227.2**. Reduction of the oxime using borane pyridine complex yields the hydroxylamine **227.3**. Exposure of the hydroxylamine to gaseous HCl followed by phosgene yields a carbamoyl chloride which is transformed to the N-hydroxyurea **227.4** with aqueous ammonia (US 4,873,259). Protection of the N-hydroxyurea may be not be necessary, but to avoid subsequent alkylation on this group, the OH is blocked with a benzyl group. Removal of the phenolic protecting group using TBAF exposes the necessary handle for placement of the pro-drug group. Treatment of the phenol with a base such as NaH or Cs₂CO₃ in solvents such as DMF or THF followed by addition of phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, **1986**, *27*, 1477) yields the desired phosphonate pro-drug. Final deblocking of the N-hydroxyurea can be achieved by hydrogenolysis conditions as described in US 4,873,259.

Example 228 Preparation of a Representative Compound of the Invention

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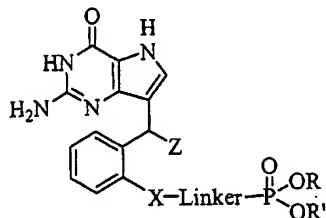
Representative compounds of the invention can be prepared as illustrated above. A specific compound of the invention can be prepared as follows.



10

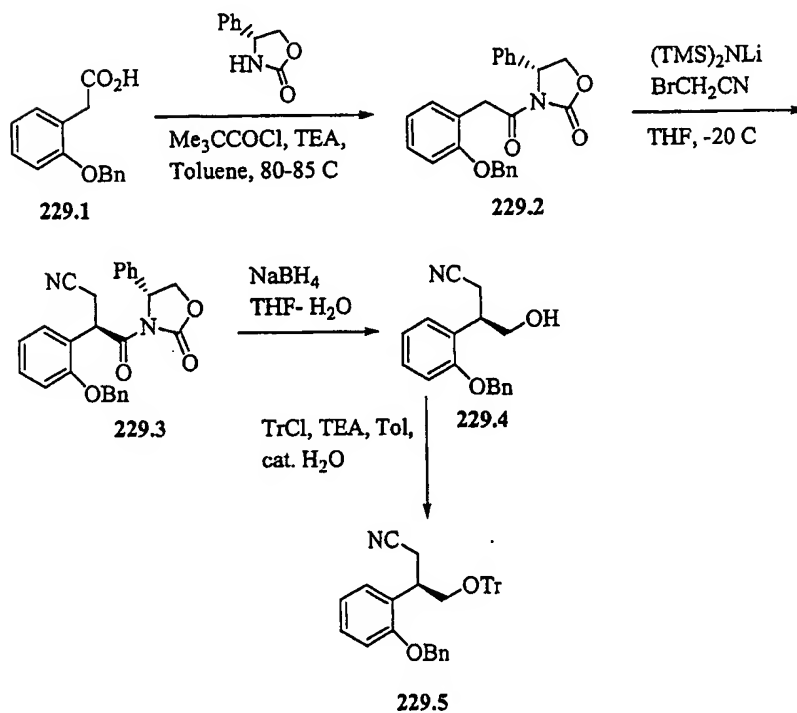
PNP-405 is prepared according to the method of Littler, B. J. et al., 7th International Conference on Organic Process Research and Development, New Orleans, LA, March 16-19, 2003. PNP-405 is treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride.

15 When bubbling ceases, diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, 1986, 27, 1477) is added, to provide compound 228.1 as the desired product.

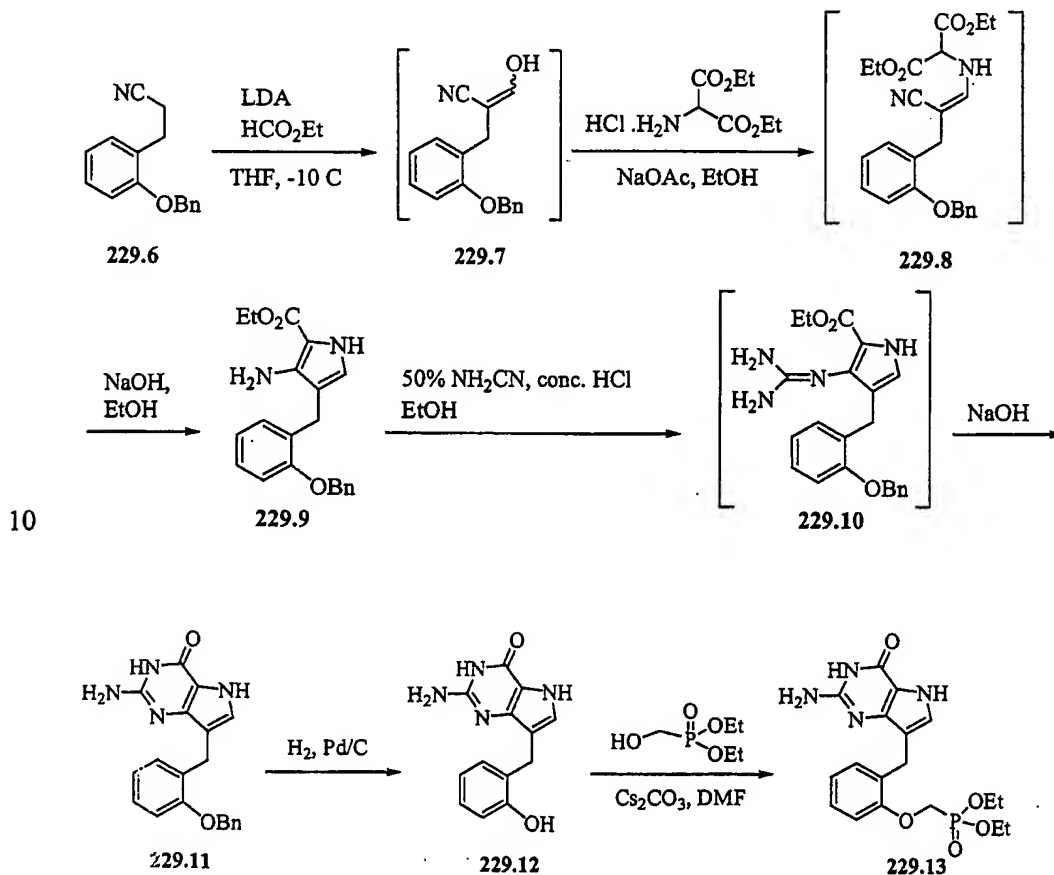
Example 229 Preparation of a Representative Compound of the Invention

Representative compounds of the general formula above (where X= O,
 5 Z= CH₂OH) can be prepared using procedures similar to those described by
 Littler, B. J. et al., 7th International Conference on Organic Process Research and
 Development, New Orleans, LA, March 16-19, 2003. A specific compound of
 the invention can be prepared as follows.

10



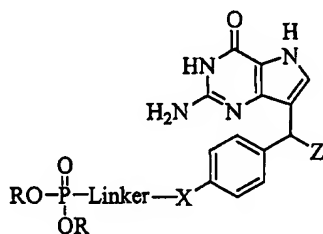
The starting material, 2-benzyloxyphenylacetic acid (provided by Avocado) can be acylated via the mixed anhydride with the oxazolidinone shown at 80-85 °C, with triethylamine as base. A low-temperature alkylation with bromoacetonitrile results in the formation of compound **229.3** with good diastereomeric ratio. Removal of the chiral auxiliary under reductive conditions yields compound **229.4** without racemization. Protection of the resulting alcohol with the trityl group provides compound **229.5**. Subsequent pyrrole ring construction as well as cyclo-guanidinylation reaction to prepare the six-membered 2-aminopyrimidone ring is performed as described below.



15 The starting material, 3-(2-Benzyloxy-phenyl)-propionitrile, is available by Lewis acid-mediated reaction of phenol with acrylonitrile according to US 2,789,995, published in 1954. Formation of 3-hydroxy-acrylonitrile **229.7** can be achieved by exposure of **229.6** to LDA and ethyl formate. Condensation of

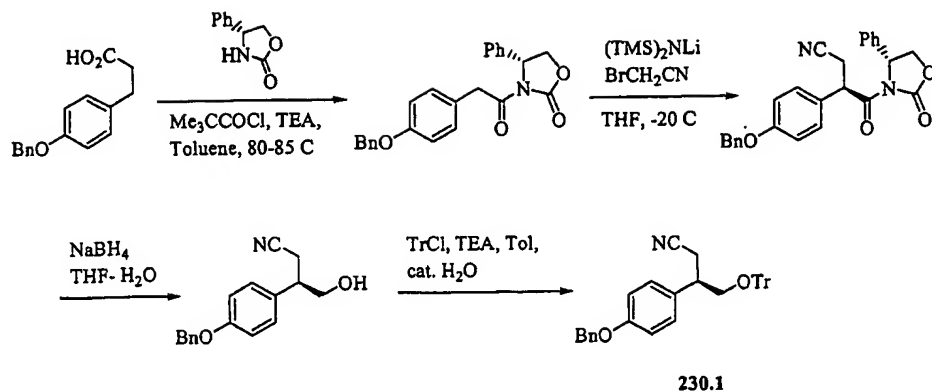
this product with 2-amino-malonic acid diethyl ester in EtOH and sodium acetate yields compound **229.8** which undergoes a decarboxylative cyclization in the basic medium of NaOH and EtOH to provide pyrrole **229.9**. The trityl protecting group on the benzylic alcohol is removed at this stage. Subsequently, 5 guanidinylation reaction using cyanamide provides compound **229.10** which, upon treatment with sodium hydroxide, cyclizes to form the 2-aminopyrimidone ring (compound **229.11**). Removal of the phenolic protecting group under hydrogenolysis conditions provides the free phenol, which is used as the attachment site for the pro-drug group. A variety of linkers may be utilized to 10 attach the phosphonate containing moiety to the backbone molecule. A particular example in which diethyl phosphonomethyltriflate is used as the starting materials is shown. Compound **229.12** is treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride or cesium carbonate. When bubbling ceases, diethyl phosphonomethyltriflate 15 (prepared according to *Tetrahedron Lett.*, **1986**, 27, 1477) is added, to provide compound **229.13** as the desired product.

Example 230 Preparation of a Representative Compound of the Invention



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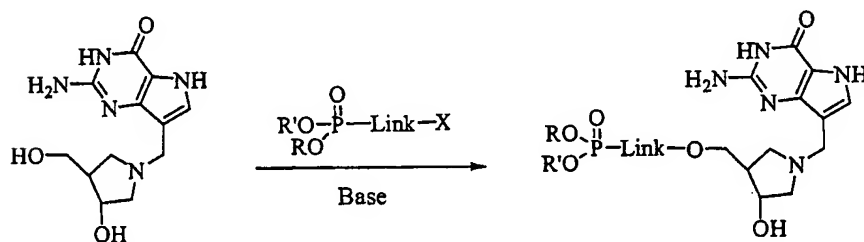
Representative compounds of the general formula above (where $\text{X} = \text{O}$, and $\text{Z} = \text{CH}_2\text{OH}$) can be prepared from 4-benzyloxyphenylacetic acid (available from Aldrich). The preparation of a specific compound of the invention is 25 described below.



Following a similar sequence to that demonstrated in Example 229, intermediate **230.1** can be prepared. Proceeding with the sequence shown in

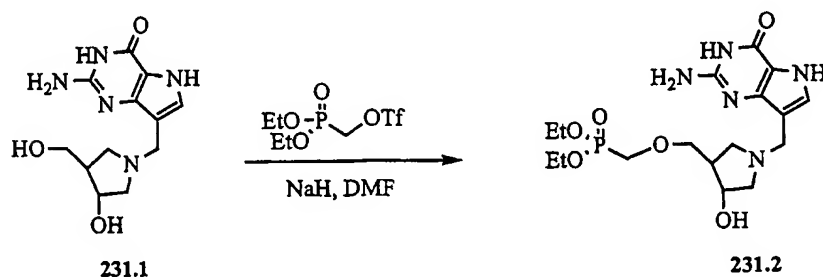
5 Example 229, **230.1** can be transformed to the desired product.

Example 231 Preparation of a Representative Compound of the Invention



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Representative compounds of the invention can be prepared as illustrated above. A specific compound of the invention can be prepared as follows.

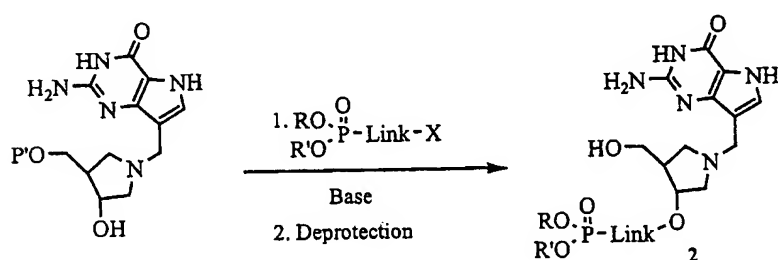


15

Preparation of DADMe-ImmG is reported in Lewandowics A. et al., *Biochemistry*, **2003**, *42*, 6057. The tertiary nitrogen of the ring may not interfere with the alkylation of the secondary alcohol and in that case does not need to be

protected, although standard protection and deprotection protocols as described in Greene, T. Protective groups in organic synthesis, Wiley-Interscience, 1999 may be used if necessary. Reaction of the primary alcohol **231.1** with base followed by addition of the appropriately activated phosphonate yields the protected product. Global deprotection yields the desired phosphonate **231.2**.

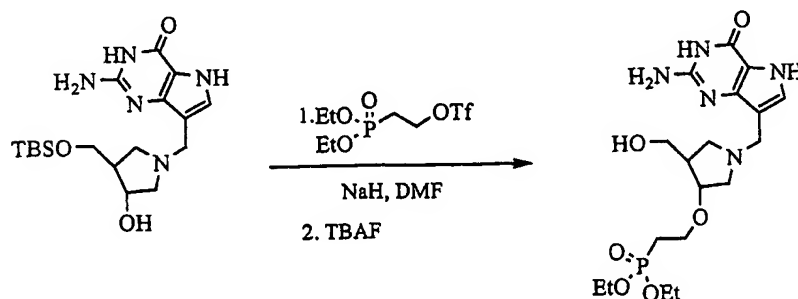
Example 232 Preparation of a Representative Compound of the Invention



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Representative compounds of the invention can be prepared as illustrated above. Preparation of DADMe-ImmG is reported in Lewandowics A. et al., *Biochemistry*, **2003**, *42*, 6057. Blocking of the primary alcohol can be achieved by methods described in Greene, T., Protective groups in organic synthesis, Wiley-Interscience, 1999. Reaction of the secondary alcohol in base followed by addition of the appropriately activated phosphonate yields the protected desired product. Deprotection yields the desired phosphonate. A specific compound of the invention can be prepared as follows.

15

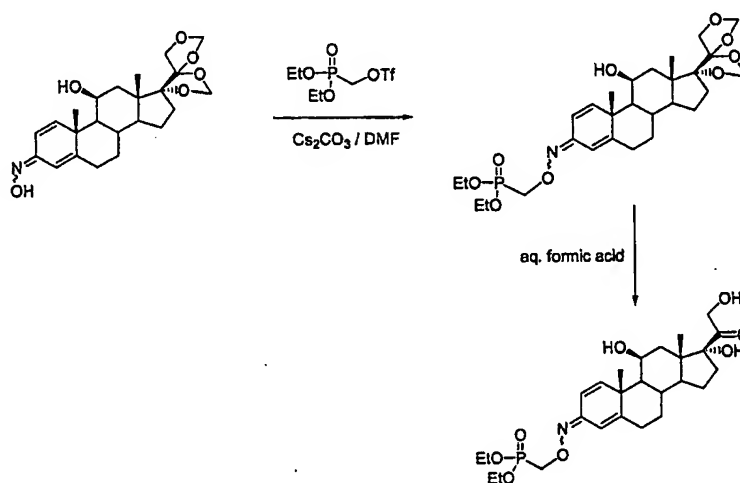


20

Specifically, the protected DADMe derivative can be treated with treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl phosphonoethyltriflate (prepared according to *Tetrahedron Lett.*, **1986**, 27, 1477) is added, yielding the desired phosphonate ester. Removal of the protecting group can be performed as described in Greene, T., *Protective groups in organic synthesis*, Wiley-Interscience, 1999 to provide the desired phosphonate ester.

Example 233 Preparation of a Representative Compound of the Invention

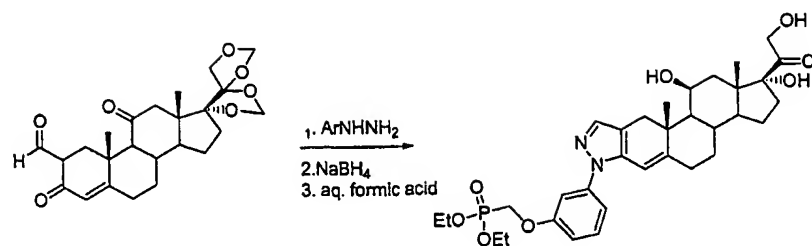
10



Representative compounds of the invention can be prepared as illustrated above. *O*-Alkylation of the oxime can be carried out by mixing the oxime and Cs_2CO_3 (ca. 1:1.2) in DMF at 0 °C for about 30 minutes with stirring. Addition of the triflate (1.2 eq.) followed by deprotection (*J. Med. Chem.* **2002**, 45, 5397) provides the compound.

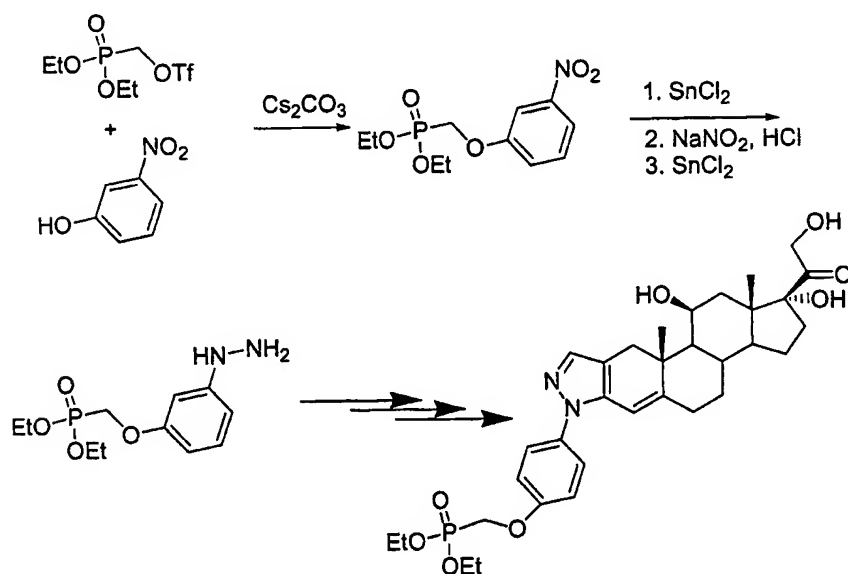
Example 234 Preparation of a Representative Compound of the Invention

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Representative compounds of the invention can be prepared as illustrated above. The pyrazole can be formed using a procedure similar to that described in
5 *J. Med. Chem.* **2002**, *45*, 5397.

Example 235 Preparation of a Representative Compound of the Invention



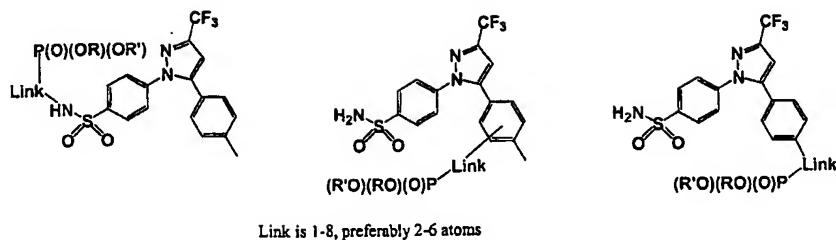
10

Representative compounds of the invention can be prepared as illustrated above. The hydrazine can be converted to the compound of the invention using a procedure similar to that described in Example 234.

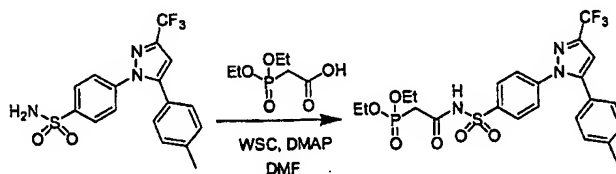
15

Examples 236-240

The preparation of the following representative compounds of the invention is illustrated in Examples 236-240.

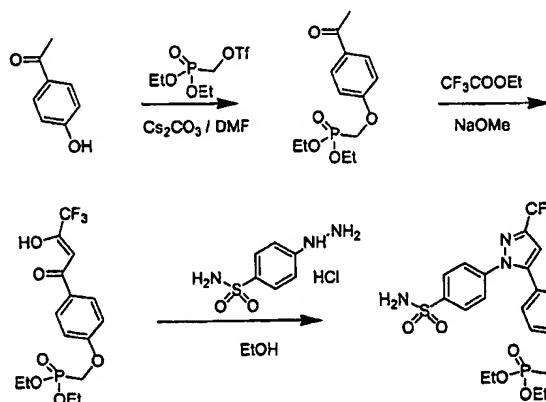


5 Example 236 Preparation of a Representative Compound of the Invention



Representative compounds of the invention can be prepared as illustrated
10 above.

Example 237 Preparation of a Representative Compound of the Invention

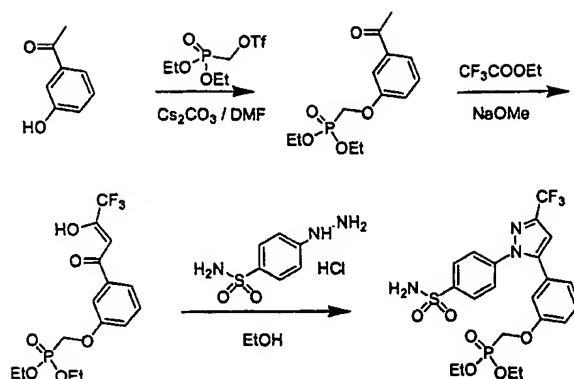


15

Representative compounds of the invention can be prepared as illustrated
above. The pyrazole can be prepared as described in *J. Med. Chem.* 1997, 40,
1347.

20

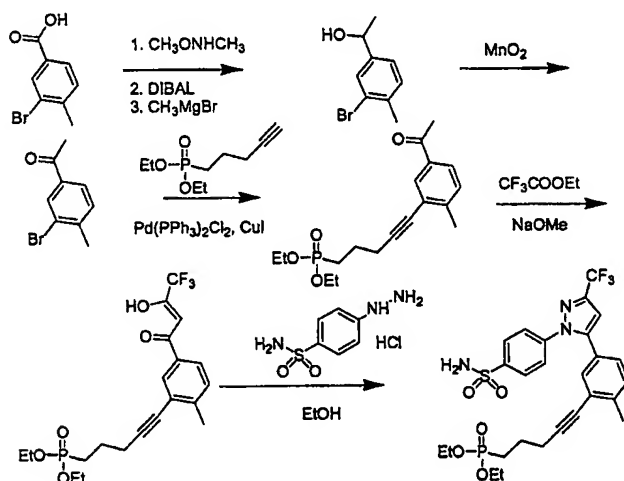
Example 238 Preparation of a Representative Compound of the Invention



Representative compounds of the invention can be prepared as illustrated above.

5

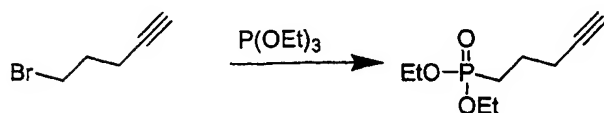
Example 239 Preparation of a Representative Compound of the Invention

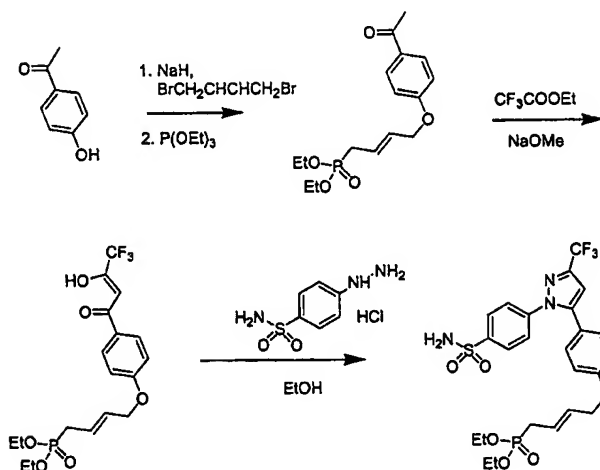


10

Representative compounds of the invention can be prepared as illustrated above.

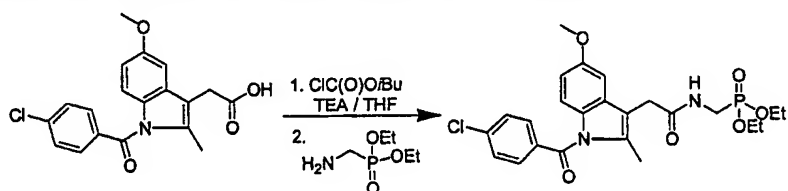
The intermediate alkyne can be prepared as follows.



Example 240 Preparation of a Representative Compound of the Invention

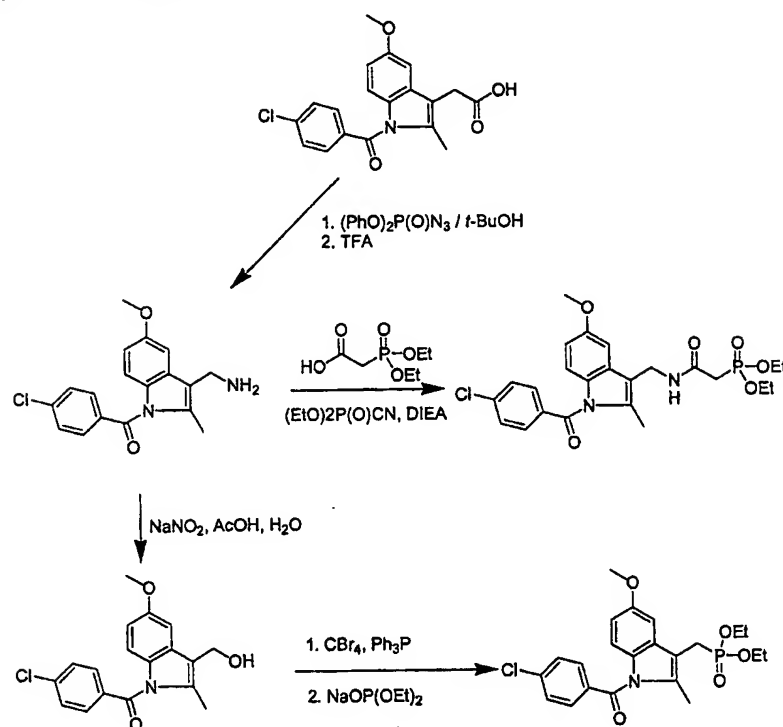
5

Representative compounds of the invention can be prepared as illustrated above.

Example 241 Preparation of a Representative Compound of the Invention

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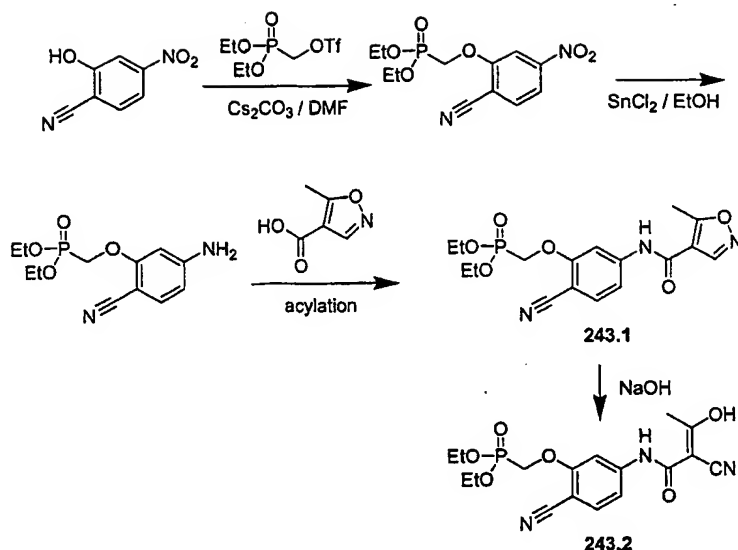
Representative compounds of the invention can be prepared as illustrated above.

Example 242 Preparation of Representative Compounds of the Invention

Representative compounds of the invention can be prepared as illustrated above.

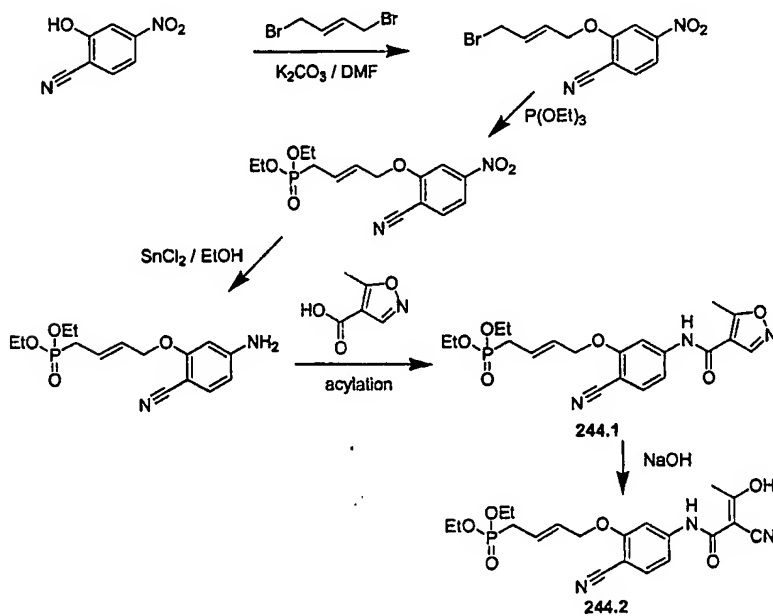
5

Example 243 Preparation of Representative Compounds of the Invention



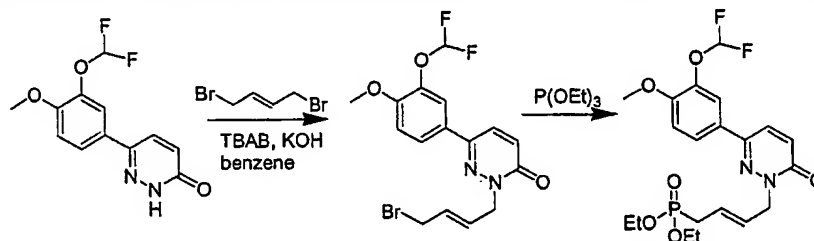
Representative compounds of the invention can be prepared as illustrated above using procedures similar to those described in *J. Med. Chem.* **1996**, *39*, 4608. Treatment of compound of the invention **243.1** with base provides compound **243.2** which is also a compound of the invention.

Example 244 Preparation of Representative Compounds of the Invention



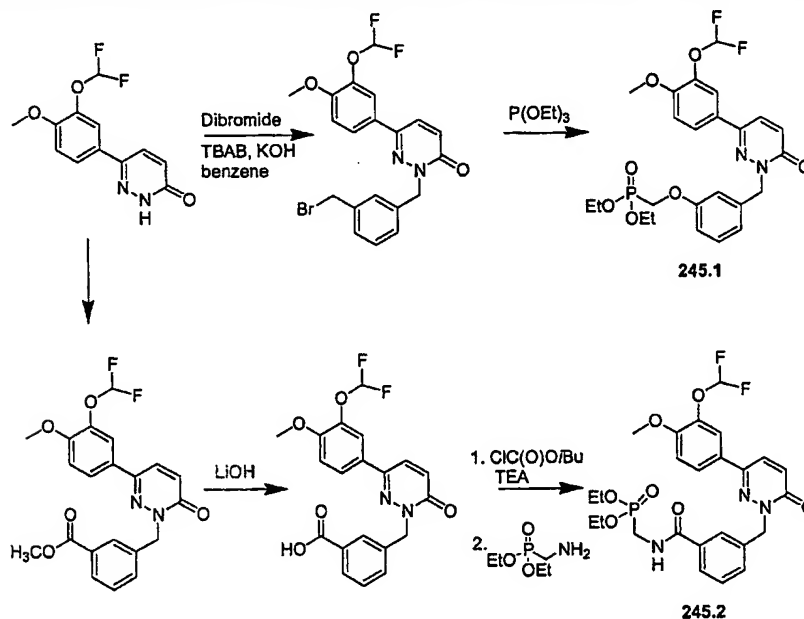
Representative compounds of the invention can be prepared as illustrated above. Treatment of compound of the invention 244.1 with base provides compound 244.2 which is also a compound of the invention.

5 Example 245 Preparation of Representative Compounds of the Invention

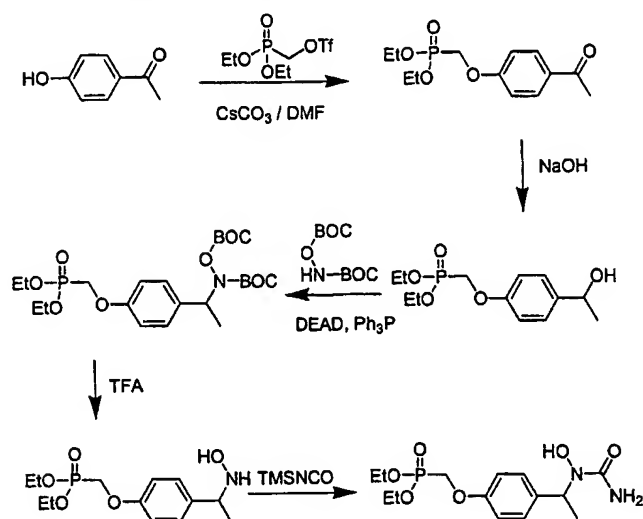


Representative compounds of the invention can be prepared as illustrated above. The *N*-alkylation of 6-aryl-3-pyridazinones is described in *J. Med. Chem.*
 10 1983, 26, 373.

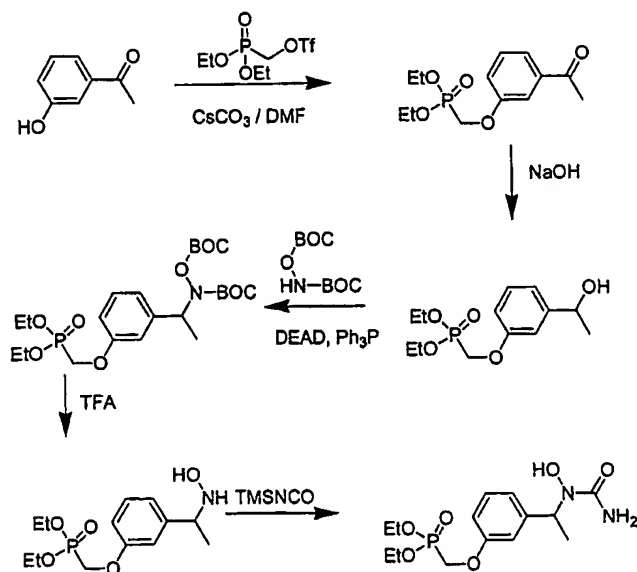
Example 246 Preparation of Representative Compounds of the Invention



Representative compounds of the invention (245.1 and 245.2) can be
 15 prepared as illustrated above.

Example 247 Preparation of Representative Compounds of the Invention

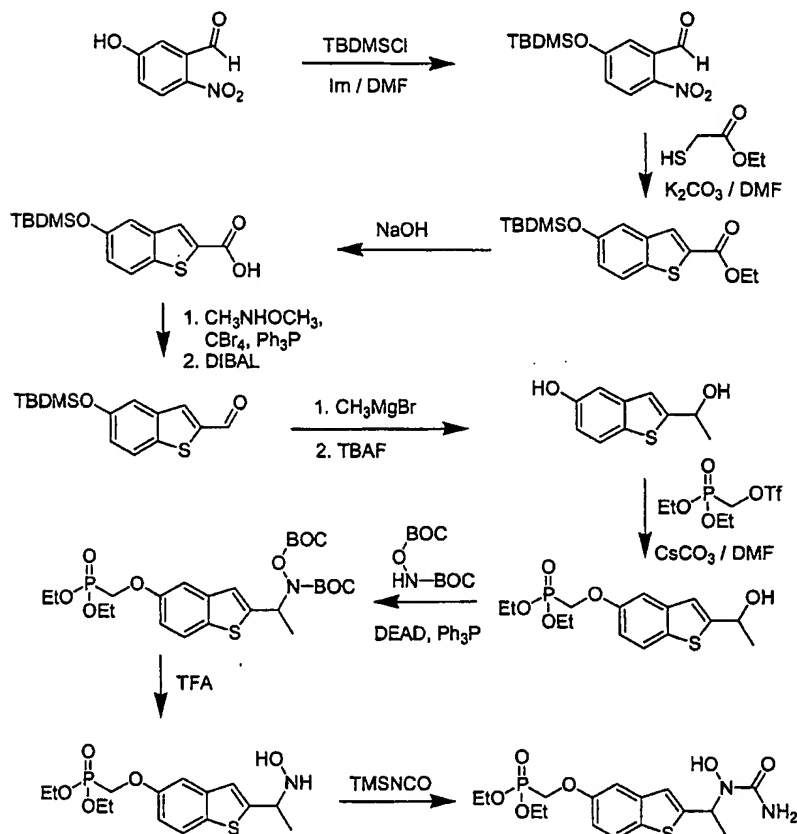
Representative compounds of the invention can be prepared as illustrated
 5 above. The synthesis of *N*-hydroxyureas is described in *J. Med. Chem.* **1997**, *40*,
 1955.

Example 248 Preparation of Representative Compounds of the Invention

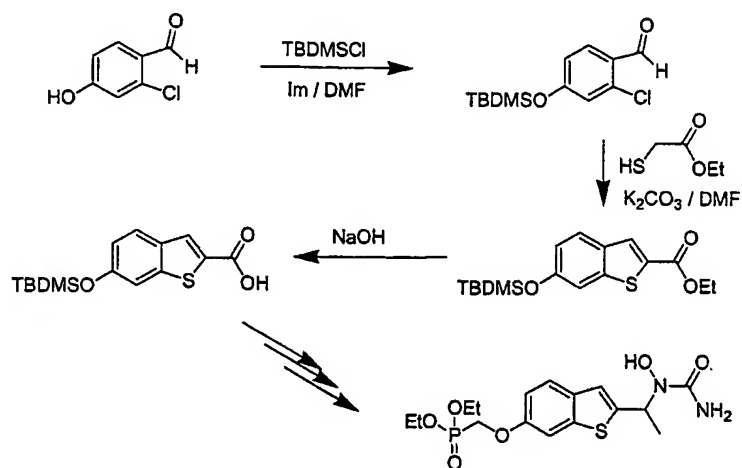
Representative compounds of the invention can be prepared as illustrated above.

Example 249 Preparation of Representative Compounds of the Invention

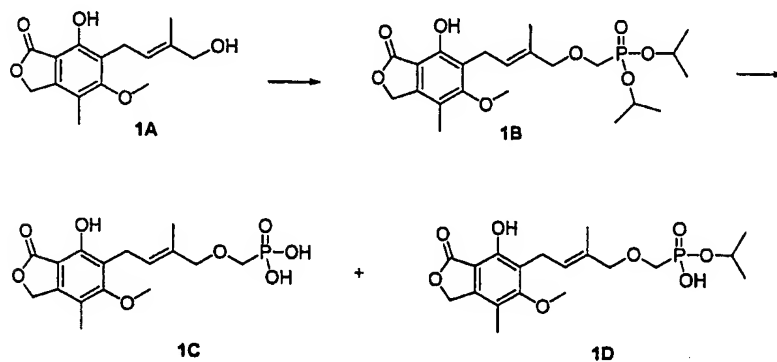
5



Representative compounds of the invention can be prepared as illustrated above.

Example 250 Preparation of Representative Compounds of the Invention

Representative compounds of the invention can be prepared as illustrated
 5 above. The synthesis of substituted benzothiophenes is described in *J. Med. Chem.* 2000, 43, 690.

Example 251: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated
 above.

[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-
 15 2-methyl-but-2-enyloxymethyl]-phosphonic acid diisopropyl ester

A mixture of 7-hydroxy-6-(4-hydroxy-3-methyl-but-2-enyl)-5-methoxy-4-methyl-3H-isobenzofuran-1-one **1A** (50 mg, 0.18 mmol, Pankiewicz *et al.*, *J. Med. Chem.*, **45**, 703), diisopropyl bromomethylphosphonate (93 mg, 0.36 mmol) and lithium *t*-butoxide (1M in THF, 0.54 mL) in DMF (3 mL) was heated at 70 °C for 5 hours. The reaction was quenched with 1N HCl. The mixture was poured into 5 % aqueous lithium chloride, extracted with ethyl acetate, and concentrated. The residue was purified by chromatography on silica gel, affording [4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid diisopropyl ester **1B** (25 mg, 32%); ¹H NMR (300 MHz, CDCl₃) δ 1.25 (m, 12H), 1.79 (s, 3H), 2.05 (s, 3H), 3.37 (d, *J* = 6.6 Hz, 2H), 3.58 (d, 2H), 3.77 (s, 3H), 3.97 (m, 2H), 4.68 (m, 2H), 5.19 (s, 2H), 5.45 (t, *J* = 6.6 Hz, 1H), 7.83 (s, 1H) ppm.

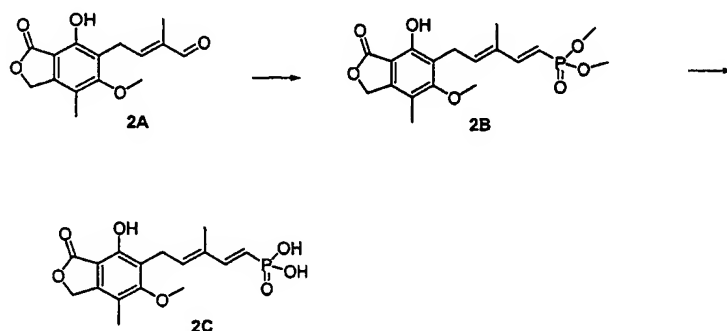
[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid and [4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid monoisopropyl ester

To a solution of [4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid diisopropyl ester **1B** (25 mg, 0.055 mmol) and 2,6-lutidine (0.18 mL, 1.65 mmol) in acetonitrile was added trimethylsilyl bromide (0.126 mL, 1.1 mmol) at 0°C. The mixture was allowed to warm to room temperature and stirred for 4 hours. The reaction was quenched with methanol at 0°C, and the resulting mixture was concentrated. The residue was purified by preparative reverse-phase HPLC to afford, after removal of the solvent, [4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid **1C** as an oil (17 mg, 83 %); ¹H NMR (300 MHz, CD₃OD) δ 1.81 (s, 3H), 2.06 (s, 3H), 3.40 (d, *J* = 6.6 Hz, 2H), 3.50 (d, 2H), 3.77 (s, 3H), 3.97 (s, 2H), 5.20 (s, 2H), 5.47 (t, *J* = 6.6 Hz, 1H) and [4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid monoisopropyl ester **1D** as an oil (2 mg, 7 %); ¹H NMR (300 MHz, CD₃OD) δ 1.23 (d, 6H), 1.81 (s, 3H), 2.08 (s, 3H), 3.40 (d,

$J = 6.6$ Hz, 2H), 3.50 (d, 2H), 3.77 (s, 3H), 3.90 (s, 2H), 4.50 (m, 1H), 5.20 (s, 2H), 5.47 (t, $J = 6.6$ Hz, 1H) ppm.

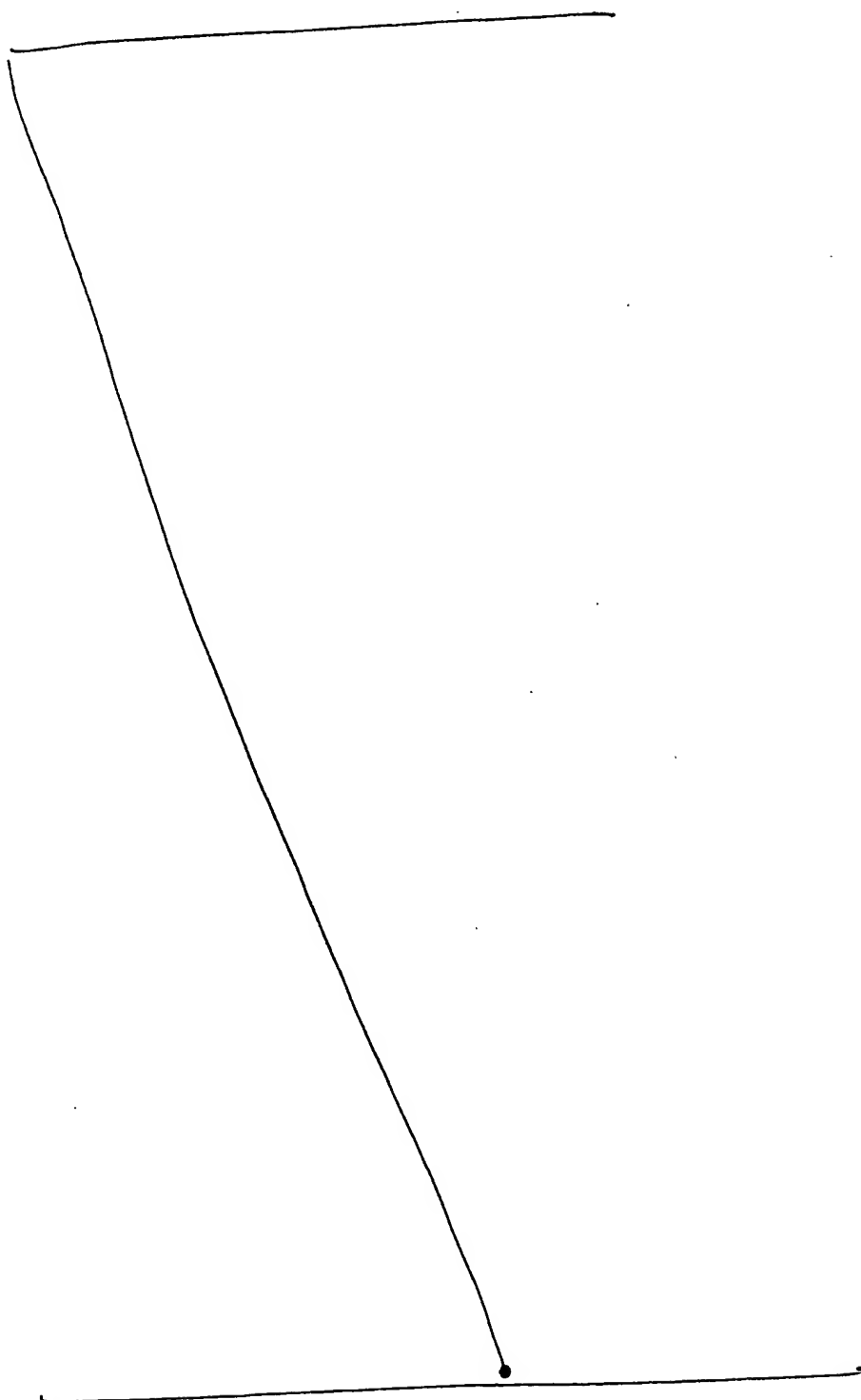
Example 252: Preparation of Representative Compounds of the Invention.

5 Representative compounds of the invention can be prepared as illustrated below.



10 **[5-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-penta-1,3-dienyl]-phosphonic acid dimethyl ester**

To a solution of tetramethylmethylene diphosphonate (102 mg, 0.44 mmol) in THF (2.5 mL) was added a THF solution of sodium bis(trimethylsilyl)amide (1.0 M, 0.44 mL). After stirring for 30 minutes, a solution of 4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enal 2A (30 mg, 0.11 mmol, Pankiewicz *et al.*, *J. Med. Chem.*, 45, 703) in THF (2.5 mL) was added, and stirring was continued for an additional 15 minutes. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate. After evaporation of solvent, the residue was purified by chromatography on silica gel eluting with ethyl acetate (50 % to 100 %) / hexanes, affording [5-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-penta-1,3-dienyl]-phosphonic acid dimethyl ester 2B (30 mg, 71 %) as an oil; ^1H NMR (300 MHz, CDCl_3) δ 1.80 (s, 3H), 2.04 (s, 3H), 3.45 (d, $J = 6.6$ Hz, 2H), 3.76 (s, 3H), 3.88 (d, 6H), 5.20 (s, 3H), 5.55 (m, 1H), 5.95 (m, 1H), 7.05 (m, 1H), 7.65 (s, 1H) ppm.

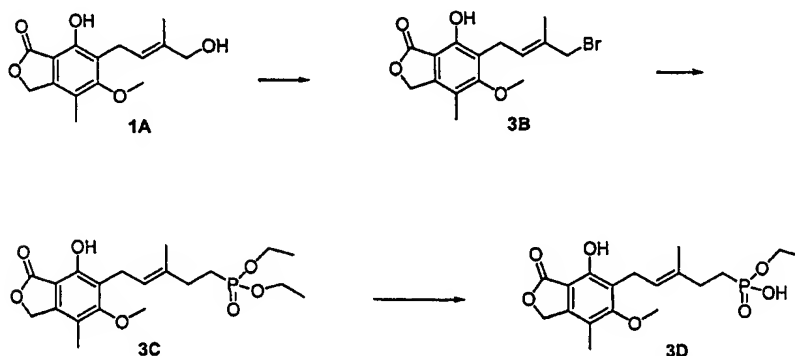


[5-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-penta-1,3-dienyl]-phosphonic acid

To a solution of [5-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-penta-1,3-dienyl]-phosphonic acid dimethyl ester 2B (22 mg, 0.057 mmol) and 2,6-lutidine (0.22 mL, 1.71 mmol) in acetonitrile was added trimethylsilyl bromide (0.183 mL, 1.71 mmol) at 0°C. The mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched with methanol at 0°C, and the resulting mixture was concentrated. The residue was purified by preparative reverse-phase HPLC to afford, after removal of the solvent, [5-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-penta-1,3-dienyl]-phosphonic acid 2C as a solid (13 mg, 65 %); ¹H NMR (300 MHz, CD₃OD) δ 1.91 (s, 3H), 2.10 (s, 3H), 3.55 (d, *J* = 6.6 Hz, 2H), 3.75 (s, 3H), 5.2 (s, 2H), 5.6-5.8 (m, 2H), 6.9 (m, 1H) ppm.

Example 253: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.



6-(4-Bromo-3-methyl-but-2-enyl)-7-hydroxy-5-methoxy-4-methyl-3H-isobenzofuran-1-one

Polymer-supported triphenylphosphine (3 mmol/g, 0.5 g) was soaked in dichloromethane (10mL) for 1 hour. 7-Hydroxy-6-(4-hydroxy-3-methyl-but-2-enyl)-5-methoxy-4-methyl-3H-isobenzofuran-1-one 1A (100 mg, 0.36 mmol) and carbon tetrabromide (143 mg, 0.43 mmol) were sequentially added and the

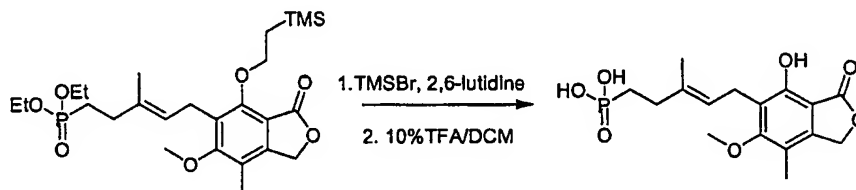
mixture was shaken for 1 hour at room temperature. More carbon tetrabromide (143 mg, 0.43 mmol) was added and the mixture was shaken further for 1 hour. The mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel (0 % to 60 % ethyl acetate / hexanes) to afford 6-
5 (4-bromo-3-methyl-but-2-enyl)-7-hydroxy-5-methoxy-4-methyl-3H-isobenzofuran-1-one 3B as an oil (52 mg, 42 %); ^1H NMR (300 MHz, CDCl_3) δ 1.95 (s, 3H), 2.16 (s, 3H), 3.44 (d, $J = 7.2$ Hz, 2H), 3.78 (s, 3H), 3.98 (s, 2H), 5.21 (s, 2H), 5.68 (t, $J = 7.2$ Hz, 1H), 7.71 (brs, 1H) ppm.

10 **[5-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-pent-3-enyl]-phosphonic acid diethyl ester**

n-Butyl lithium (1.6 M in hexanes, 1 mL) was added to an equal volume of THF at -20°C . A solution of diethyl methylphosphonate (220 mg, 1.45 mmol) in THF (1 mL) was then added dropwise and the solution was stirred for 30
15 minutes. After cooling at -60°C , the solution was transferred *via* a cannula to a vial containing copper (I) iodide (276 mg, 1.45 mmol), and the resulting mixture was stirred for 1 hour at -30°C . A solution of 6-(4-bromo-3-methyl-but-2-enyl)-7-hydroxy-5-methoxy-4-methyl-3H-isobenzofuran-1-one 3B (50 mg, 0.15 mmol) in THF (1 mL) was added and the mixture was allowed to warm to 0°C
20 for 2 hours before saturated aqueous ammonium chloride was added. The reaction mixture was acidified with 2 N HCl and extracted with ethyl acetate. The ethyl acetate extract was concentrated and the residue was chromatographed on silica gel (40% to 100% ethyl acetate / hexanes), affording [5-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-pent-3-
25 enyl]-phosphonic acid diethyl ester 3C as an oil (27 mg, contaminated with the starting diethyl methylphosphonate); ^1H NMR (300 MHz, CDCl_3) δ 1.32 (m, 6H), 1.8-1.9 (m, 5H), 2.18 (s, 3H), 2.25 (m, 2H), 3.42 (d, $J = 7.2$ Hz, 2H), 3.78 (s, 3H), 4.15 (m, 4H), 5.21 (s, 2H), 5.24 (t, $J = 7.2$ Hz, 1H), 7.65 (s, 1H) ppm.

[5-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-pent-3-enyl]-phosphonic acid monoethyl ester

A mixture of [5-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-pent-3-enyl]-phosphonic acid diethyl ester 3C (27 mg, 0.066 mmol), LiOH (200 mg), MeOH (3 mL) and water (1 mL) was stirred at 70°C for 4 hours. After cooling, the reaction solution was acidified with 2 N HCl, mixed with brine, and extracted with ethyl acetate / acetonitrile. The organic extract was concentrated and the residue was purified by preparative reverse-phase HPLC (acetonitrile and 0.1% aqueous CF₃COOH), affording [5-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-pent-3-enyl]-phosphonic acid monoethyl ester 3D (7 mg, 28 %); ¹H NMR (300 MHz, CD₃OD) δ 1.28 (t, *J* = 6.9 Hz, 3H), 1.7-1.9 (m, 5H), 2.20 (s, 3H), 2.2-2.3 (m, 2H), 3.41 (d, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 4.02 (m, 2H), 5.2-5.3 (m, 3H) ppm.



[5-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-pent-3-enyl]-phosphonic acid

To a solution of {5-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-sobenzofuran-5-yl]-3-methyl-pent-3-enyl}-phosphonic acid diethyl ester (20 mg, 0.039 mmol) in DMF (0.5 mL) and DCM (0.5 mL) was added TMSBr (50.5 μL, 0.39 mmol) followed by 2,6-lutidine (45.3 μL, 0.39 mmol). The reaction was allowed to proceed for one hour when it was complete, as judged by LCMS. The reaction mixture was quenched with MeOH and concentrated to dryness. The residue was purified by preparative reverse-phase HPLC. The fraction containing the desired product was concentrated and treated with 10% TFA/DCM for 5 minutes. After concentration, the residue was purified by preparative reverse-phase HPLC to provide 7 mg (50%) of [5-(4-Hydroxy-6-

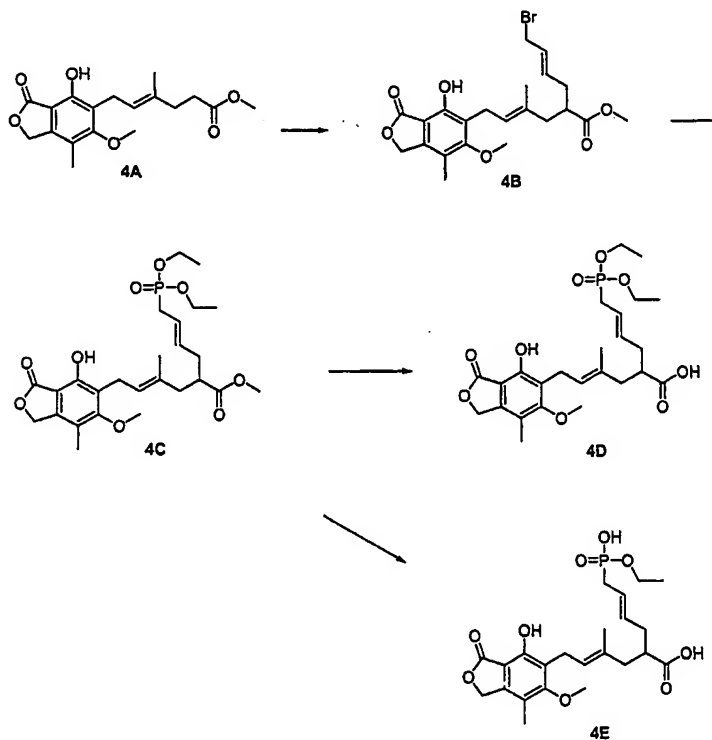
methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-pent-3-enyl]-phosphonic acid as a solid. ^1H NMR (300 MHz, CD_3OD) δ 1.66-1.78 (m, 5H), 2.10 (s, 3H), 2.16-2.22 (m, 2H), 3.34 (d, $J = 7.2$ Hz, 2H), 3.72 (s, 3H), 5.16 (s, 2H), 5.20 (t, $J = 7.2$ Hz, 1H) ppm; ^{31}P (121.4 MHz, CD_3OD) δ 31.57 ppm;

5 MS (m/z) 355 $[\text{M}-\text{H}]^-$, 357 $[\text{M}+\text{H}]^+$.

Example 254: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.

10



2-(4-Bromo-but-2-enyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid methyl ester

15 To a cooled (-78°C) solution of mycophenolic acid methyl ester 4A (138 mg, 0.41 mmol) in THF (2.5 mL) was added a THF solution of sodium bis(trimethylsilyl)amide (1.0 M, 0.98 mL). After stirring for 30 minutes, a solution of 1,4-dibromo-2-butene (950 mg, 4.1 mmol) in THF (2.5 mL) was

added and stirring was continued for 10 minutes. The resulting mixture was warmed to -30°C and stored at this temperature for 16 hours. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate to give, after evaporation of the solvent, a residue
 5 that was purified by chromatography on silica gel eluting with ethyl acetate (0 % to 40 %) / hexanes, affording 2-(4-bromo-but-2-enyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid methyl ester **4B** (150 mg, 78 %) as an oil; ^1H NMR (300 MHz, CDCl_3) δ 1.75 (s, 3H), 2.0-2.4 (m, 8H), 2.62 (m, 1H), 3.37 (d, $J = 6.6$ Hz, 2H), 3.58 (s, 3H), 3.76
 10 (s, 3H), 3.88 (d, $J = 4.8$ Hz, 2H), 5.1-5.3 (m, 3H), 5.67 (brs, 2H), 7.67 (s, 1H) ppm.

2-[4-(Diethoxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid methyl ester
 15

A solution of 2-(4-bromo-but-2-enyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid methyl ester **4B** (140 mg, 0.30 mmol) and triethylphosphite (600 mg, 3.6 mmol) in toluene (30 mL) was stirred at reflux for 20 hours. The mixture was
 20 concentrated and chromatographed on silica gel eluting with ethyl acetate (60 % to 100 %) / hexanes, affording 2-[4-(diethoxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid methyl ester **4C** as an oil (70 mg, 43 %); ^1H NMR (300 MHz, CDCl_3) δ 1.27 (m, 6H), 1.79 (s, 3H), 2.0-2.7 (m, 8H), 3.37 (d, $J = 6.6$ Hz), 3.52
 25 (s, 3H), 3.75 (s, 3H), 4.08 (m, 4H), 5.20 m, 3H), 5.45 (m, 2H) ppm.

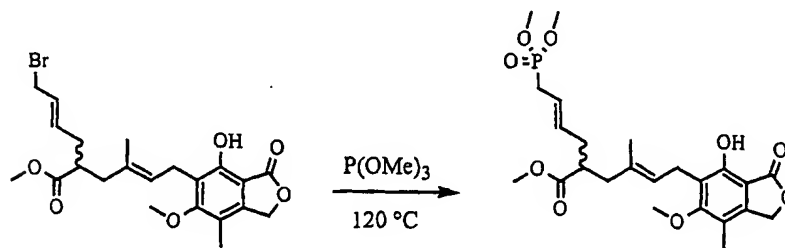
2-[4-(Diethoxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid

A mixture of 2-[4-(diethoxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid methyl ester **4C** (33 mg, 0.063 mmol) and lithium hydroxide (44 mg) in a
 30

mixture of THF (6 mL) and water (1 mL) was stirred at room temperature for 6 hours. The organic solvent was removed and the residue was partitioned between ethyl acetate and 5 % aqueous sodium bicarbonate. The aqueous layer was acidified with 2 N HCl and extracted with ethyl acetate. The ethyl acetate
 5 extract was concentrated, affording 2-[4-(diethoxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid **4D** as an oil (30 mg, 100%); ^1H NMR (300 MHz, CDCl_3) δ 1.27 (m, 6H), 1.79 (s, 3H), 2.0-2.7 (m, 8H), 3.37 (d, $J = 6.6$ Hz), 3.75 (s, 3H), 4.08 (m, 4H), 5.19 (s, 2H), 5.25 (m, 1H), 5.44 (m, 1H), 5.55 (m, 1H), 5.45 (m,
 10 2H) ppm.

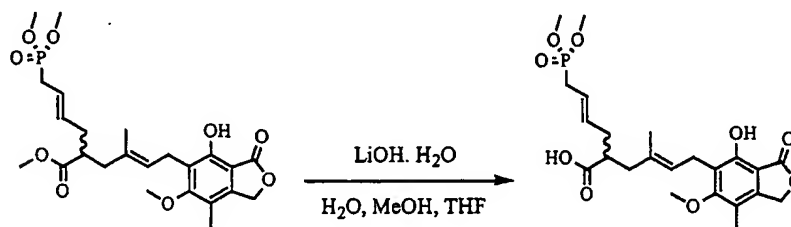
2-[4-(Ethoxy-hydroxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid

A mixture of 2-[4-(diethoxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic
 15 acid methyl ester **4C** (25 mg, 0.048 mmol) and lithium hydroxide (200 mg) in a mixture of methanol (3 mL) and water (1 mL) was stirred at 70°C for 2 hours. The organic solvent was evaporated and the residue acidified with 2N HCl and extracted with ethyl acetate /acetonitrile. The organic extract was concentrated,
 20 and the residue was purified by preparative reverse-phase HPLC (acetonitrile and 0.1% aqueous CF_3COOH), affording 2-[4-(ethoxy-hydroxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid **4E** as an oil (15 mg, 89%); ^1H NMR (300 MHz, CD_3OD) δ 1.25 (t, $J = 6.9$ Hz, 3H), 1.81 (s, 3H), 2.1-2.6 (m, 8H), 3.40 (d, $J = 6.6$ Hz, 2H), 3.77 (s, 3H), 3.97 (m, 2H), 5.1-5.3 (m, 3H), 5.67 (brs, 2H) ppm.



2-[4-(Dimethoxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid methyl ester

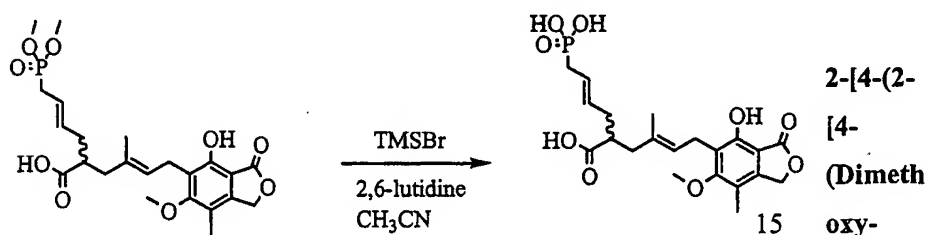
- 5 Under a N₂ atmosphere, a solution of 2-(4-bromo-but-2-enyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid methyl ester (490 mg, 1.05 mmol) in trimethylphosphite (2.5 mL, 21.1 mmol) was heated at 120°C for 1 hour. The reaction was allowed to cool to room temperature. The reaction mixture was worked up by removal of
- 10 the solvent *in vacuo* followed by chromatography using EtOAc-hexanes to provide 460 mg (88%) of the product as an oil. ¹H NMR (300 MHz, CDCl₃) δ 1.77 (s, 3H), 2.081- 2.31 (m, 4H), 2.15 (s, 3H), 2.52 (d, 1H, *J*= 22 Hz), 2.54 (d, 1H, *J*= 22 Hz), 2.55- 2.63 (m, 1H), 3.36 (d, 2H, *J*= 7 Hz), 3.57 (s, 3H), 3.72 (d, 6H, *J*= 11 Hz), 3.76 (s, 3H), 5.20 (s, 2H), 5.20- 5.26 (m, 1H), 5.36- 5.56 (m,
- 15 2H), 7.69 (s, 1H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 30.1 ppm; MS (*m/z*) 497.2 [M+H]⁺, 519.2 [M+Na]⁺.



- 20 **2-[4-(Dimethoxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid**
- 2-[4-(Dimethoxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid methyl ester (460 mg, 0.927 mmol) in a solution of 1: 1: 2 of H₂O, MeOH, THF
- 25 (8 mL) was stirred with LiOH·H₂O (78 mg, 1.86 mmol) at ambient temperature for 12 hours. A second batch of LiOH·H₂O (40 mg, 0.952 mmol) was added. The reaction mixture was stirred at room temperature for another 16 hours, after

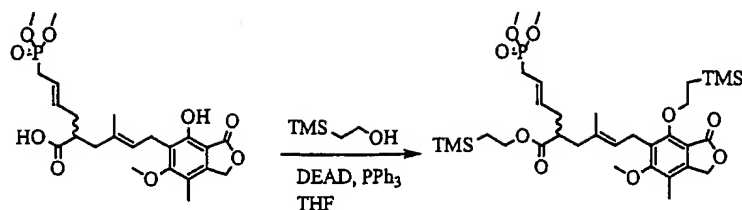
which no further progress was observed. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl . The organic layer was removed *in vacuo* and the product was extracted with EtOAc from the aqueous layer, which had been acidified by addition of 5 drops of 2 N HCl. The product was further purified by chromatography to provide the desired product. ^1H NMR (300 MHz, CDCl_3) δ 1.79 (s, 3H), 2.08-2.38 (m, 4H), 2.15 (s, 3H), 2.53 (d, 1H, J = 22 Hz), 2.60 (d, 1H, J = 22 Hz), 2.57- 2.64 (m, 1H), 3.38 (d, 2H, J = 7 Hz), 3.72 (d, 6H, J = 11 Hz) 3.76 (s, 3H), 5.20 (s, 2H), 5.27 (t, 1H, J = 6 Hz), 5.36- 5.63 (m, 2H) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 30.5 ppm; MS (m/z) 481.2 [$\text{M}-\text{H}$].

10



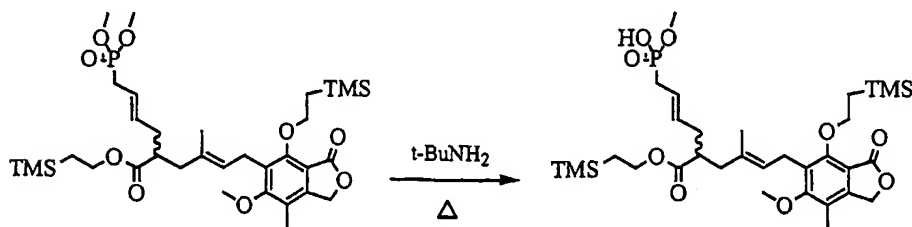
phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid

To a solution of 2-[4-(dimethoxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid (25 mg, 0.052 mmol) in acetonitrile (2 mL) was added 2,6-lutidine (60 μ L, 0.52 mmol) and TMSBr (67 μ L, 0.52 mmol). The reaction was allowed to proceed for 45 minutes when it was completed as judged by LCMS. The reaction mixture was concentrated under reduced pressure and quenched with an aqueous NaOH solution (1 mL). The product was purified by RP HPLC (using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA) to provide 14.2 mg (60%) of the product as a solid. ¹H NMR (300 MHz, CD₃OD) δ 1.81 (s, 3H), 2.081- 2.31 (m, 4H), 2.16 (s, 3H), 2.45 (d, 1H, *J* = 22 Hz), 2.47 (d, 1H, *J* = 22 Hz), 2.55- 2.63 (m, 1H), 3.38 (d, 2H, *J* = 7 Hz), 3.77 (s, 3H), 5.25 (s, 2H), 5.20- 5.36 (m, 1H), 5.36- 5.56 (m, 2H) ppm; ³¹P (121.4 MHz, CD₃OD) δ 25.4 ppm; MS (*m/z*) 453 [M-H]⁺.



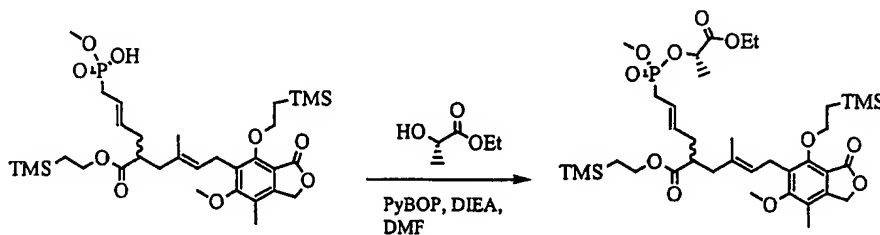
2-[4-(Dimethoxy-phosphoryl)-but-2-enyl]-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilyl-ethyl ester

A solution of 2-[4-(dimethoxy-phosphoryl)-but-2-enyl]-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid (160 mg, 0.332 mmol) and trimethylsilylethanol (160 mg, 1.36 mmol) in THF (8.00 mL) was stirred with triphenylphosphine (345 mg, 1.33 mmol). To this solution was added diethyl azodicarboxylate (230 μ L, 1.33 mmol) at 0°C. The mixture was allowed to warm to room temperature and stirred for 16 hours. Additional triphenylphosphine (180 mg, 0.692 mmol), trimethylsilylethanol (160 mg, 1.36 mmol), and diethyl azodicarboxylate (115 μ L, 0.665 mmol) were added and the reaction mixture was stirred for another 1 day at room temperature. The reaction was worked up by removing the solvents *in vacuo* and purifying the residue by silica gel chromatography to provide 192 mg (85%) of the product as a clear oil. ^1H NMR (300 MHz, CDCl_3) δ 0.03 (s, 9H), 0.05 (s, 9H), 0.93-0.96 (m, 2H), 1.20-1.29 (m, 2H), 1.78 (s, 3H), 2.01-2.32 (m, 4H), 2.17 (s, 3H), 2.51 (d, 1H, $J=22$ Hz), 2.58 (d, 1H, $J=22$ Hz), 2.50-2.60 (m, 1H), 3.37 (d, 2H, $J=7$ Hz), 3.72 (d, 6H, $J=11$ Hz), 3.76 (s, 3H), 4.08 (appt t, 2H, $J=8$ Hz), 4.30 (appt t, 2H, $J=8$ Hz), 5.12 (s, 2H), 5.15-5.25 (m, 1H), 5.36-5.63 (m, 2H) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 29.3 ppm; MS (m/z) 705.3 $[\text{M}+\text{Na}]^+$.



2-[4-(Hydroxy-methoxy-phosphoryl)-but-2-enyl]-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilylanyl-ethyl ester

A mixture of 2-[4-(dimethoxy-phosphoryl)-but-2-enyl]-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilylanyl-ethyl ester (184 mg, 0.270 mmol) in *tert*-butylamine (2.8 mL, 27 mmol) was heated at 60 °C for 24 hours. The solution was allowed to cool to room temperature and concentrated. The residue was purified by silica gel column chromatography using MeOH/ CH₂Cl₂ (0-30%) to provide 75 mg of the product as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ 0.01 (s, 9H), 0.04 (s, 9H), 0.89 (appt t, 2H, *J*= 9 Hz), 1.23 (appt t, 2H, *J*= 9 Hz), 1.77 (s, 3H), 2.01- 2.31 (m, 4H), 2.17 (s, 3H), 2.36 (d, 1H, *J*= 22 Hz), 2.38 (d, 1H, *J*= 22 Hz), 2.52 (septet, 1H, *J*= 9 Hz), 3.39 (d, 2H, *J*= 7 Hz), 3.51 (d, 3H, *J*= 11 Hz), 4.01- 4.08 (m, 2H), 4.30 (dd, 2H, *J*= 8, 9 Hz), 5.11 (s, 2H), 5.19 (br t, 1H, *J*= 6 Hz), 5.33- 5.56 (m, 2H), 8.49 (br s, 1H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 22.1 ppm; MS (*m/z*) 667.4 [M+Na]⁺.

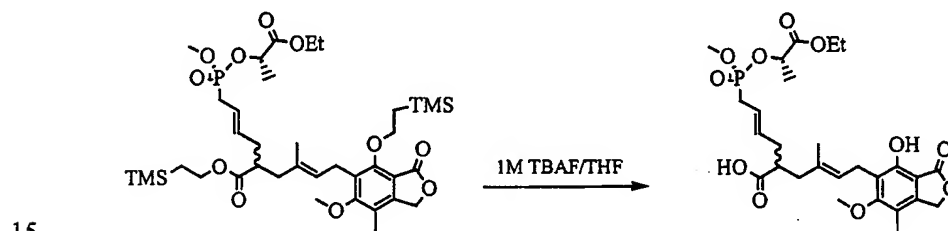


2-[4-[(1-Ethoxycarbonyl-ethoxy)-methoxy-phosphoryl]-but-2-enyl]-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilylanyl-ethyl ester

A solution of 2-[4-(hydroxy-methoxy-phosphoryl)-but-2-enyl]-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilylanyl-ethyl ester (67 mg, 0.10 mmol) and PyBOP (234 mg, 0.450 mmol) in DMF (1.5 mL) was stirred with ethyl (S)-(-)-lactate (53 mg, 0.45 mmol) and DIEA (174 μL, 1.00 mmol) at ambient temperature for 1 hour, when complete consumption of the

starting materials was observed. The reaction was worked up by addition of saturated aqueous sodium chloride and ethyl acetate. The organic layer was separated and washed with 5% aqueous solution of lithium chloride. The organic layer was dried *in vacuo* and the residue was purified by silica gel

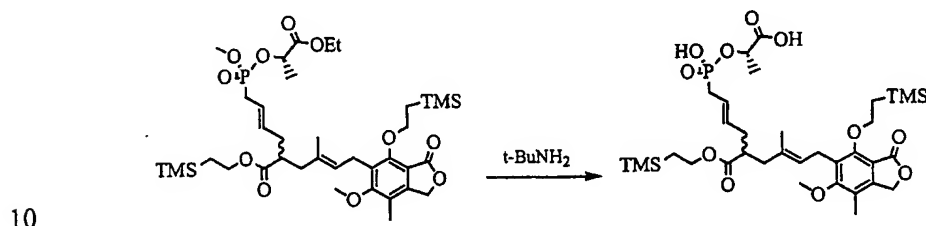
5 chromatography using MeOH-CH₂Cl₂ (0-20%) to provide 57 mg (74%) of the desired product as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ 0.02 (s, 9H), 0.05 (s, 9H), 0.88- 0.94 (m, 2H), 1.20- 1.30 (m, 2H), 1.29 (t, 3H, *J*= 7 Hz), 1.45 (d, 3H, *J*= 7 Hz), 1.78 (s, 3H), 2.01- 2.31 (m, 4H), 2.17 (s, 3H), 2.50- 2.58 (m, 1H), 2.65 (d, 1H, *J*= 22 Hz), 2.67 (d, 1H, *J*= 22 Hz), 3.39 (d, 2H, *J*= 7 Hz), 3.69 and
10 3.77 (d, 3H, *J*= 11 Hz), 3.76 (s, 3H), 4.07 (appt t, 2H, *J*= 7 Hz), 4.20 (dq, 2H, *J*= 3, 7 Hz), 4.29 (appt t, 2H, *J*= 9 Hz), 4.85- 4.99 (m, 1H), 5.12 (s, 2H), 5.19 (br t, 1H, *J*= 6 Hz), 5.33- 5.61 (m, 2H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 28.9, 29.9 ppm; MS (*m/z*) 791.4 [M+Na]⁺.



2-{4-[(1-Ethoxycarbonyl-ethoxy)-methoxy-phosphoryl]-but-2-enyl}-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid

20 A solution of 2-{4-[(1-ethoxycarbonyl-ethoxy)-methoxy-phosphoryl]-but-2-enyl}-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilyl-ethyl ester (14 mg, 0.018 mmol) in THF (1 mL) was stirred with a 1M solution of TBAF in THF (55 μL, 0.055 mmol) for 1 hour. The reaction mixture was
25 concentrated, acidified with 1N HCl and extracted with EtOAc. The organic layer was washed with brine and dried. The product was purified by silica gel column chromatography EtOH-EtOAc (0-10%). Further purification was performed by dissolving the product in CH₂Cl₂ and passing the compound

through a 13 mm Acrodisc syringe filter with a 0.45 μm Nylon membrane to provide 8 mg (77%) of the product. ^1H NMR (300 MHz, CDCl_3) δ 0.92 (t, 3H, $J=7$ Hz), 1.30 (d, 3H, $J=8$ Hz), 1.79 (s, 3H), 2.10- 2.39 (m, 4H), 2.15 (s, 3H), 2.53 (d, 1H, $J=8$ Hz), 2.65 (d, 1H, $J=22$ Hz), 2.68 (d, 1H, $J=22$ Hz), 3.38 (d, 2H, $J=7$ Hz), 3.70 and 3.74 (d, 3H, $J=11$ Hz), 3.76 (s, 3H), 4.07 (m, 2H), 4.96 (dq, 1H, $J=7$ Hz), 5.20 (s, 2H), 5.27 (br t, 1H, $J=7$ Hz), 5.33- 5.55 (m, 2H), 7.51- 7.56 (m, 1H), 7.68- 7.74 (m, 1H) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 29.0, 30.1 ppm; MS (m/z) 569.2 $[\text{M}+\text{H}]^+$, 591.3 $[\text{M}+\text{Na}]^+$.

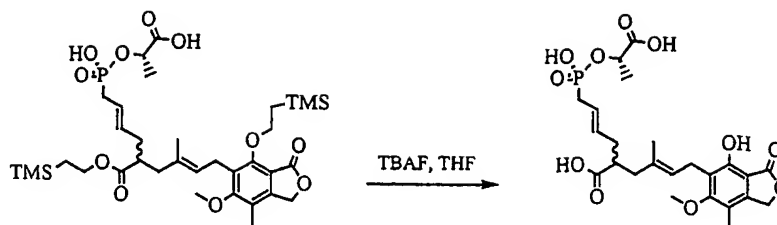


2-{4-[(1-Carboxy-ethoxy)-hydroxy-phosphoryl]-but-2-enyl}-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilanyl-ethyl ester

15 A solution of 2-{4-[(1-ethoxycarbonyl-ethoxy)-methoxy-phosphoryl]-but-2-enyl}-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilanylethyl ester (12 mg, 0.016 mmol) in *tert*-butylamine (1 mL, 9.6 mmol) was heated at 65°C for 16 hours. The solution was allowed to cool to room temperature and

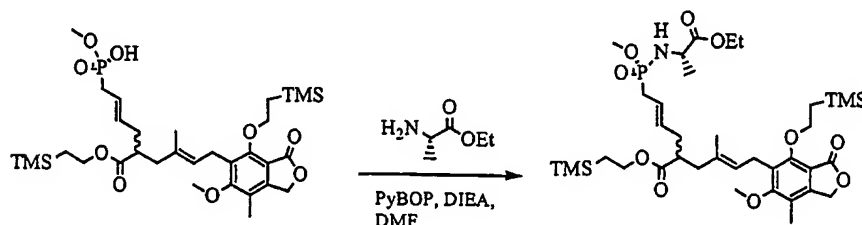
20 concentrated to provide the crude product as an oil. ^1H NMR (300 MHz, CDCl_3) δ 0.03 (s, 9H), 0.04 (s, 9H), 0.86- 0.98 (m, 2H), 1.22- 1.33 (m, 2H), 1.50 (d, 3H, $J=7$ Hz), 1.78 (s, 3H), 2.05- 2.30 (m, 4H), 2.10 (s, 3H), 2.48- 2.63 (m, 3H), 3.40 (d, 2H, $J=7$ Hz), 3.76 (s, 3H), 4.08 (appt t, 2H, $J=9$ Hz), 4.25- 4.33 (m, 2H), 4.75- 4.84 (m, 1H), 5.13 (s, 2H), 5.15- 5.23 (m, 1H), 5.33- 5.55 (m, 2H) ppm;

25 ^{31}P (121.4 MHz, CDCl_3) δ 28.9 ppm; MS (m/z) 725.3 $[\text{M}-\text{H}]^-$.



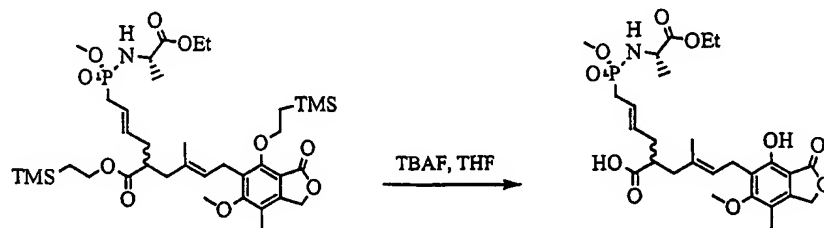
2-{4-[(1-Carboxy-ethoxy)-hydroxy-phosphoryl]-but-2-enyl}-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid

A solution of crude 2-{4-[(1-carboxy-ethoxy)-hydroxy-phosphoryl]-but-2-enyl}-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilyl-ethyl ester (AC-2101-59) and tetrabutylammonium fluoride in THF (1M, 54 μ L, 0.054 mmol) was stirred with THF (1 mL) for 2 hours at ambient temperature, when more tetrabutylammonium fluoride in THF (54 μ L, 0.054 mmol) was added. The reaction was stirred for an additional 16 hours, by which time the reaction was complete. The reaction mixture was concentrated *in vacuo* and the product was purified by RP HPLC using a Phenomenex Synergi 5 μ Hydro RP 80A column (50 x 21.2 mm) with eluents of H₂O, 0.1% TFA-CH₃CN, 0.1% TFA to provide the product (8.0 mg) as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ 1.51 (d, 3H, *J* = 7 Hz), 1.79 (s, 3H), 2.05- 2.40 (m, 4H), 2.11 (s, 3H), 2.49- 2.71 (m, 3H), 3.38 (d, 2H, *J* = 6 Hz), 3.76 (s, 3H), 4.85 (br s, 1H), 5.20 (s, 2H), 5.21- 5.30 (m, 1H), 5.33- 5.63 (m, 2H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 27.7 ppm; MS (*m/z*) 525.2 [M-H].



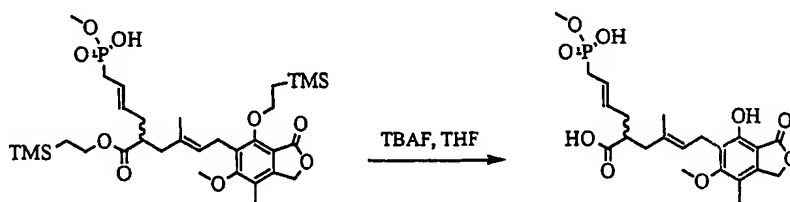
2-{4-[(1-Ethoxycarbonyl-ethylamine)-methoxy-phosphoryl]-but-2-enyl}-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilylanyl-ethyl ester

A solution of 2-[4-(hydroxy-methoxy-phosphoryl)-but-2-enyl]-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilylanyl-ethyl ester (20 mg, 0.030 mmol), PyBOP (62.4 mg, 0.120 mmol) in DMF (1.0 mL) was stirred with L-alanine ethyl ester hydrochloride (18 mg, 0.12 mmol) and DIEA (26 μ L, 0.15 mmol) at ambient temperature for 1 hour, when complete consumption of the starting materials was observed. The reaction was worked up by addition of water until the reaction solution became cloudy. DMF was added dropwise until the mixture became clear again. The reaction mixture was filtered through Acrodisc (13 mm syringe filter with a 0.45 μ m Nylon membrane) and purified by RP HPLC using a Phenomenex Synergi 5 μ Hydro RP 80A column (50 x 21.2 mm), eluting with water and acetonitrile. The fractions containing the product were pooled together and concentrated *in vacuo* to remove the acetonitrile. The remaining solution was saturated with sodium chloride and extracted with EtOAc and acetonitrile to provide 7.2 mg of the product. ^1H NMR (300 MHz, CDCl_3) δ 0.03 (s, 9H), 0.05 (s, 9H), 0.923 (appt t, 2H, $J = 8$ Hz), 1.18- 1.31 (m, 5H), 1.41 (t, 3H, $J = 7$ Hz), 1.78 (s, 3H), 2.03- 2.36 (m, 4H), 2.18 (s, 3H), 2.43- 2.63 (m, 3H), 3.10- 3.30 (m, 1H), 3.40 (d, 2H, $J = 7$ Hz), 3.62 and 3.65 (d, 3H, $J = 11$ Hz), 3.76 (s, 3H), 4.03-4.12 (m, 2H), 4.20 (dq, 2H, $J = 2, 7$ Hz), 4.29 (appt t, 2H, $J = 8$ Hz), 5.12 (s, 2H), 5.18- 5.28 (m, 1H), 5.33- 5.67 (m, 2H) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 30.4, 31.2 ppm; MS (m/z) 790.4 [$\text{M} + \text{Na}$] $^+$.



2-{4-[(1-Ethoxycarbonyl-ethylamine)-methoxy-phosphoryl]-but-2-enyl}-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid

To a solution of 2-{4-[(1-ethoxycarbonyl-ethylamine)-methoxy-phosphoryl]-but-2-enyl}-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilyl-ethyl ester (7.2 mg, 9.38 mmol) in THF (1 mL) was added TBAF (40 μ L, 1M solution in THF) at room temperature. The reaction mixture was stirred for 20 minutes, when the starting material was completely converted to the desired product as judged by LCMS. The reaction mixture was dried *in vacuo* and re-dissolved in DMF. The product was purified by RP HPLC using a Phenomenex Synergi 5 μ Hydro RP 80A column (50 x 21.2 mm) with eluents of H₂O-CH₃CN. The fractions containing the desired product were pooled and further purified on Dowex 50WX8-400 packed on a 4.5 cm x 2 cm column to elute the sodium salt at H₂O- MeOH (1:1), providing 3.2 mg of the desired product. ¹H NMR (300 MHz, CD₃OD) δ 1.26 (dd, 3H, *J* = 4, 7 Hz), 1.37 (t, 3H, *J* = 8 Hz), 1.80 (s, 3H), 2.00- 2.22 (m, 4H), 2.10 (s, 3H), 2.25- 2.60 (m, 3H), 3.37 (d, 2H, *J* = 7 Hz), 3.60 and 3.65 (d, 3H, *J* = 11 Hz), 3.74 (s, 3H), 3.83- 3.96 (m, 1H), 4.18 (q, 2H, *J* = 8 Hz), 5.15 (s, 2H), 5.25- 5.42 (m, 2H), 5.55- 5.69 (m, 1H) ppm; ³¹P (121.4 MHz, CD₃OD) δ 33.8, 34.2 ppm; MS (*m/z*) 568.2 [M+H]⁺, 590.3 [M+Na]⁺.

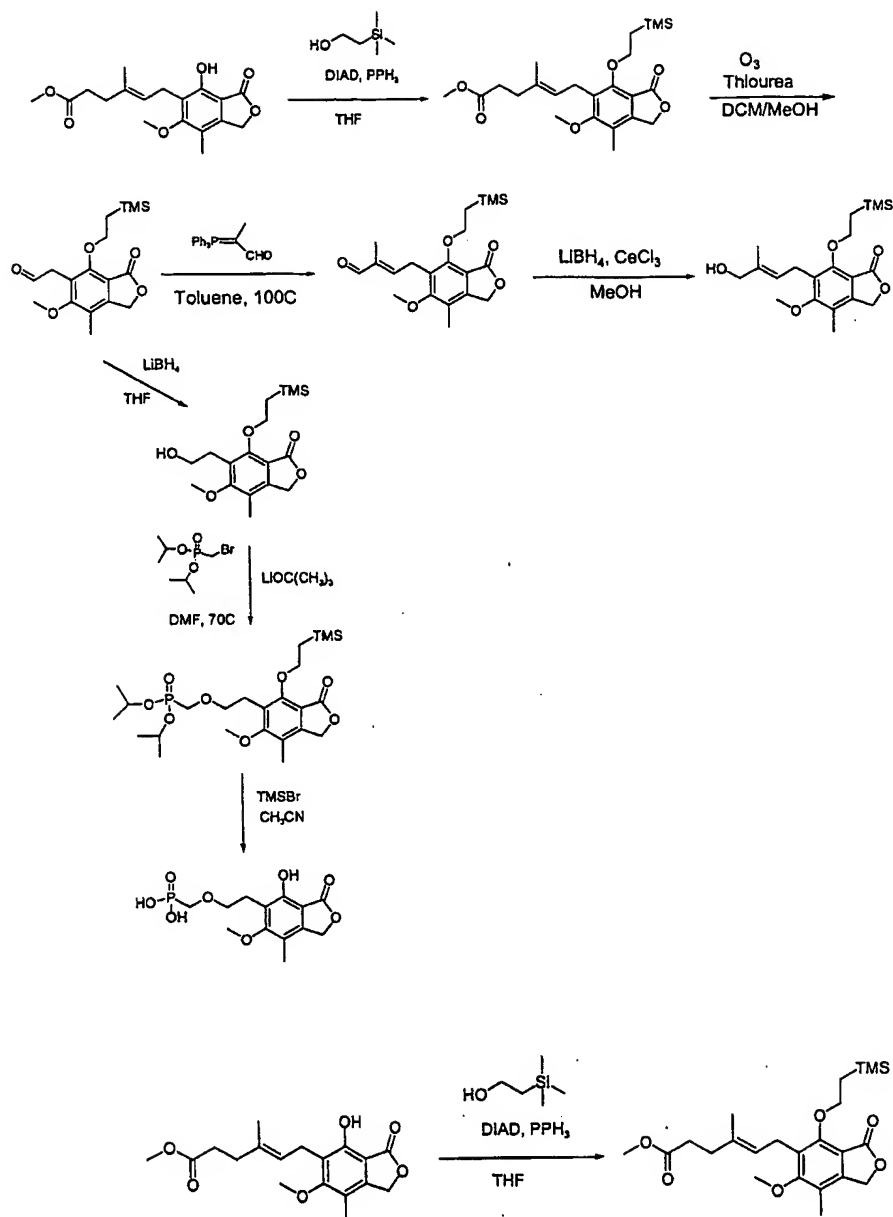


25 6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-[4-(hydroxy-methoxy-phosphoryl)-but-2-enyl]-4-methyl-hex-4-enoic acid

To a solution of 2-[4-(hydroxy-methoxy-phosphoryl)-but-2-enyl]-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid 2-trimethylsilyl-ethyl ester (11

mg, 0.016 mmol) in THF (1 mL) was added TBAF (50 μ L, 1M solution in THF) at room temperature. The solution was stirred for 16 hours and concentrated. The solution was dried under reduced pressure and re-suspended in DMF (0.8 mL) and water (0.25 mL). The solution was filtered through Acrodisc (13 mm syringe
5 filter with a 0.45 μ m Nylon membrane) and purified by RP HPLC using a Phenomenex Synergi 5 μ Hydro RP 80A column (50 x 21.2 mm) with eluents of H₂O, 0.1% TFA-CH₃CN, 0.1% TFA. The product from the column was subjected to ion exchange chromatography (Sodium salt form of Dowex 50WX8-400) using a 2 x 4.5 cm column eluting with H₂O-MeOH (1:1) to
10 provide 7.5 mg of the desired product as an oil. ¹H NMR (300 MHz, CDCl₃) δ 1.80 (s, 3H), 2.01- 2.29 (m, 5H), 2.11 (s, 3H), 2.35 (d, 2H, *J*= 22 Hz), 3.38 (d, 2H, *J*= 7 Hz), 3.53 (d, 3H, *J*= 11 Hz), 3.75 (s, 3H), 5.19 (s, 2H), 5.26 (t, 1H, *J*= 6 Hz), 5.43- 5.54 (m, 2H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 23.5 ppm; MS (*m/z*) 469.2 [M+H]⁺, 491.3 [M+Na]⁺.

15



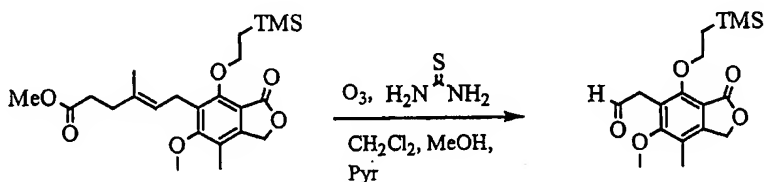
5 **6-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid methyl ester**

To a solution of 6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoic acid methyl ester (222 mg, 0.66 mmol), triphenylphosphine (260 mg, 0.996 mmol), and diethyl azodicarboxylate (173 mg, 0.996 mmol) in THF (3 mL) at 0°C was added a solution of 2-trimethylsilylethanol (142 μL, 0.996 mmol) in THF (3 mL). The resulting yellow

10

solution was allowed to warm to room temperature and stirred overnight. The reaction was concentrated to dryness and ether and hexanes were added. Triphenylphosphine oxide was removed by filtration and the filtrate was concentrated and purified by silica gel chromatography to provide 248 mg of the
 5 desired product as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 0.03 (s, 9H), 1.18- 1.30 (m, 2H), 1.81 (s, 3H), 2.18 (s, 3H), 2.25- 2.33 (m, 2H), 2.37- 2.45 (m, 2H), 3.42 (d, 2H, $J=7$ Hz), 3.62 (s, 3H), 3.77 (s, 3H), 4.25- 4.35 (m, 2H), 5.13 (s, 2H), 5.12- 5.22 (m, 1H) ppm.

10

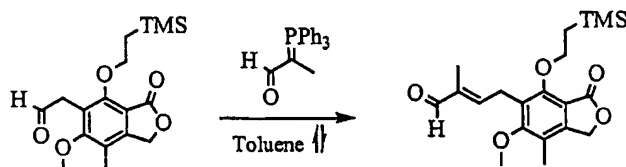


[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-acetaldehyde

A solution of 6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid methyl ester
 15 (618 mg, 1.42 mmol) in MeOH (10 mL), CH_2Cl_2 (10 mL) and pyridine (50 μL , 0.618 mmol) was cooled to -70°C using a dry ice/ acetone bath according to the procedure of Smith, D. B. *et al.*, *J. Org. Chem.*, 1996, 61, 6, 2236. A stream of ozone was bubbled through the reaction via a gas dispersion tube until the
 20 reaction became blue in color (15 minutes). The ozone line was replaced with a stream of nitrogen and bubbling continued for another 15 minutes, by which time the blue color had disappeared. To this solution, thiourea (75.7 mg, 0.994 mmol) was added in one portion at -70°C , and the cooling bath was removed. The reaction was allowed to warm to room temperature and stirred for 15 hours.
 25 The reaction was worked up by filtration to remove solid thiourea S-dioxide, and then partitioned between CH_2Cl_2 and water. The organic layer was removed. The aqueous layer was washed with CH_2Cl_2 one more time, and the organic extracts were combined. The organic layer was washed with aqueous 1N HCl, saturated NaHCO_3 and brine. The organic extracts were dried *in vacuo* and the residue

was purified to by silica gel chromatography to afford 357 mg (75 %) of the product as a white solid. ^1H NMR (300 MHz, CDCl_3) δ -0.01 (s, 9H), 1.05- 1.15 (m, 2H), 2.15 (s, 3H), 3.69 (s, 3H), 3.78 (d, 2H, J = 1 Hz), 4.27- 4.39 (m, 2H), 5.11 (s, 2H), 9.72 (d, 1H, J = 1 Hz) ppm.

5

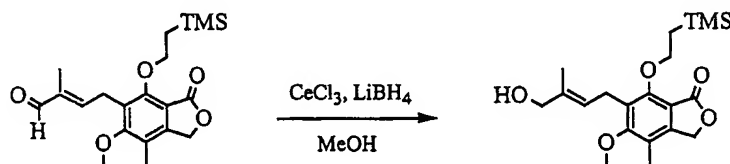


4-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enal

10 [6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-acetaldehyde (70 mg, 0.21 mmol) in toluene (2 mL) was heated at 100 °C with 2-(triphenyl-phosphanylidene)-propionaldehyde (72.9 mg, 0.23 mmol) overnight. A second portion of 2-(triphenyl-phosphanylidene)-propionaldehyde (33 mg, 0.11 mmol) was added and the reaction mixture was

15 heated for an additional day. After concentration, the residue was purified by silica gel chromatography to provide 54 mg (83%) of the desired product as a pale yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 0.00 (s, 9H), 1.10- 1.21 (m, 2H), 1.87 (s, 3H), 2.16 (s, 3H), 3.67- 3.76 (m, 2H), 3.74 (s, 3H), 4.27- 4.39 (m, 2H), 5.11 (s, 2H), 6.40- 6.48 (m, 1H), 9.2 (s, 1H) ppm.

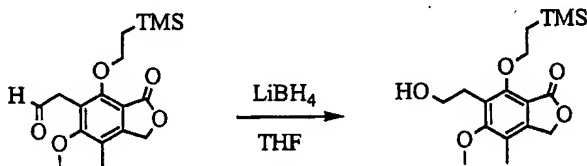
20



6-(4-Hydroxy-3-methyl-but-2-enyl)-5-methoxy-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one

25 A solution of 4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enal (103 mg, 0.27 mmol) in methanol (5 mL) was cooled to 0°C. A solution of CeCl_3 (0.68 mL,

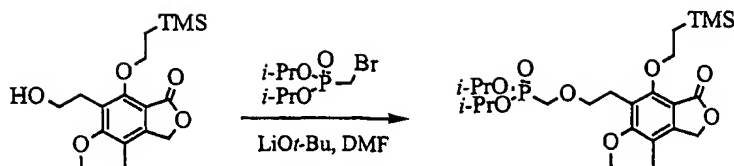
MeOH: H₂O, 9:1) was added, followed by LiBH₄ (0.14 mL, 0.28 mmol of a 2M solution in THF). The ice bath was removed and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for an additional 40 minutes whereupon TLC indicated complete consumption of starting aldehyde. The reaction was worked up by addition of aqueous 1N HCl (0.5 mL) and the product was extracted with CH₂Cl₂. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography to provide 100 mg (97%) of the product as a clear liquid. ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 9H), 1.20 (dd, 2H, *J*= 7, 8 Hz), 1.81 (s, 3H), 2.13 (s, 3H), 3.38- 3.50 (m, 2H), 3.74 (s, 3H), 3.95 (s, 2H), 4.27 (dd, 2H, *J*= 7, 8 Hz), 5.08 (s, 2H), 5.17- 5.44 (m, 1H) ppm.



15

6-(2-Hydroxy-ethyl)-5-methoxy-4-methyl-7-(2-trimethylsilylanyl-ethoxy)-3H-isobenzofuran-1-one

To a solution of [6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-acetaldehyde (97 mg, 0.29 mmol) in THF (5 mL) was added an aliquot of a 2 M LiBH₄ in THF (150 μL, 0.300 mmol). The reaction mixture was stirred at room temperature for 1 hour when complete consumption of the starting materials was observed by TLC. The reaction mixture was worked up by addition of an aqueous 1N HCl solution and extraction with EtOAc. The organic layer was dried *in vacuo* and the residue was purified by silica gel chromatography to provide the product. ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 9H), 1.20 (dd, 2H, *J*=7, 9 Hz), 2.07 (br s, 1H), 2.14 (s, 3H), 2.97 (t, 2H, *J*= 6 Hz), 3.76 (t, 2H, *J*= 6 Hz), 3.77 (s, 3H), 4.32 (dd, 2H, *J*= 7, 8 Hz), 5.08 (s, 2H) ppm.

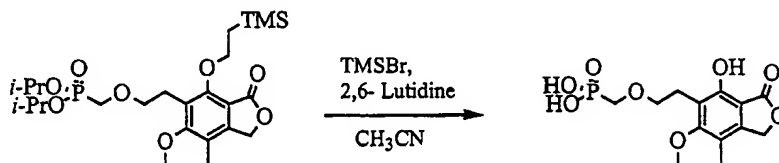


{2-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-ethoxymethyl}-phosphonic acid diisopropyl ester

- 5 A mixture of 6-(2-hydroxy-ethyl)-5-methoxy-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one (79 mg, 0.23 mmol) was heated with bromomethylphosphonic acid diisopropyl ester (120 mg, 0.46 mmol) in the presence of lithium *t*-butoxide (22 mg, 0.27 mmol) in DMF (2 mL) at 70 °C overnight. The reaction mixture was purified by RP HPLC (acetonitrile and 0.1% aqueous CF₃COOH) to provide the desired product. ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 9H), 1.13- 1.25 (m, 2H), 1.26 (t, 12H, *J*= 6 Hz), 2.12 (s, 3H), 2.98 (t, 2H, *J*= 7 Hz), 3.60- 3.73 (m, 4H), 3.77 (s, 3H), 4.05- 4.16 (m, 2H), 4.62- 4.74 (m, 2H), 5.07 (s, 2H) ppm; MS (*m/z*) 539 [M+Na]⁺.

Example 255: Preparation of Representative Compounds of the Invention.

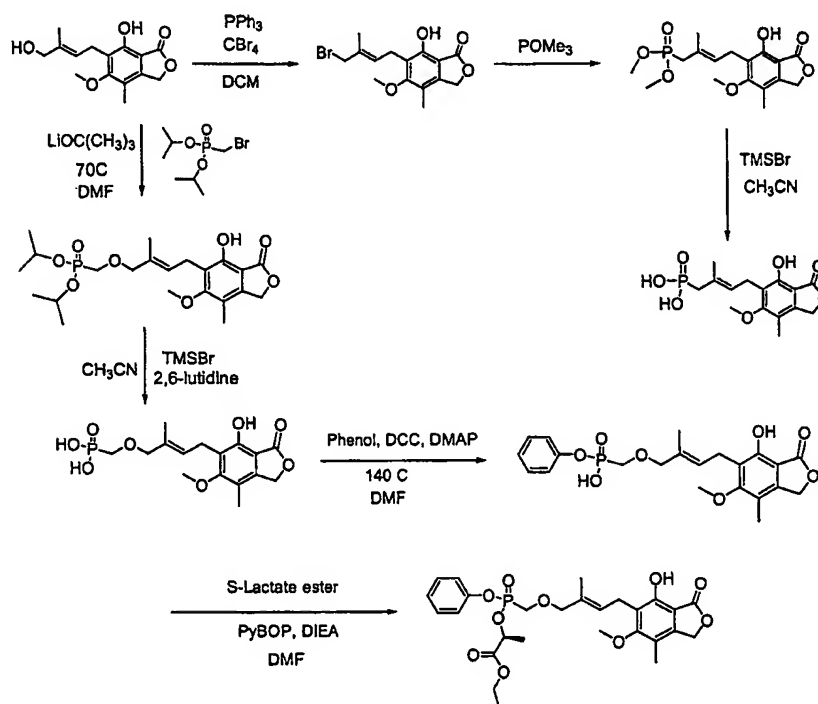
Representative compounds of the invention can be prepared as illustrated below.



[2-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-ethoxymethyl]-phosphonic acid

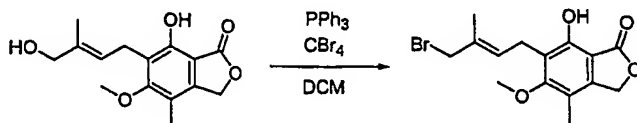
- 20 To a solution of {2-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-ethoxymethyl}-phosphonic acid diisopropyl ester (7.5 mg, 0.014 mmol) in acetonitrile (2 mL) and 2,6-lutidine (25 μL, 0.21 mmol) was added trimethylsilyl bromide (27 μL, 0.21 mmol) at room temperature. The reaction was allowed to proceed for 18 hours when completion of the reaction was indicated by LCMS. The reaction was quenched

by addition of MeOH and concentration. The residue was purified by RP-HPLC using a C18 column. The collected product was dissolved in a solution of 10% TFA/ CH₂Cl₂ to assure complete deprotection. The reaction mixture was lyophilized to provide the desired product. ¹H NMR (300 MHz, CD₃OD) δ 2.12 (s, 3H), 2.98 (t, 2H, *J* = 7 Hz), 3.66- 3.76 (m, 4H), 3.78 (s, 3H), 5.21 (s, 2H) ppm;
 5 MS (*m/z*) 331 [M-H]⁻.



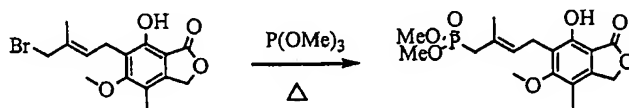
10 Example 256: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.



15 6-(4-Bromo-3-methyl-but-2-enyl)-7-hydroxy-5-methoxy-4-methyl-3H-isobenzofuran-1-one

Polymer-supported triphenylphosphine (3 mmol/g, 0.5 g) was soaked in dichloromethane (10mL) for 1 hour. 7-Hydroxy-6-(4-hydroxy-3-methyl-but-2-enyl)-5-methoxy-4-methyl-3H-isobenzofuran-1-one (100 mg, 0.36 mmol) and carbon tetrabromide (143 mg, 0.43 mmol) were added sequentially and the mixture was shaken for 1 hour at room temperature. More carbon tetrabromide (143 mg, 0.43 mmol) was added and the mixture was shaken further for 1 hour. The mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel (0 % to 60 % ethyl acetate / hexanes) to afford 6-(4-bromo-3-methyl-but-2-enyl)-7-hydroxy-5-methoxy-4-methyl-3H-isobenzofuran-1-one as an oil (52 mg, 42 %); ^1H NMR (300 MHz, CDCl_3) δ 1.95 (s, 3H), 2.16 (s, 3H), 3.44 (d, $J = 7.2$, 2H), 3.78 (s, 3H), 3.98 (s, 2H), 5.21 (s, 2H), 5.68 (t, $J = 7.2$ Hz, 1H), 7.71 (brs, 1H) ppm.



15

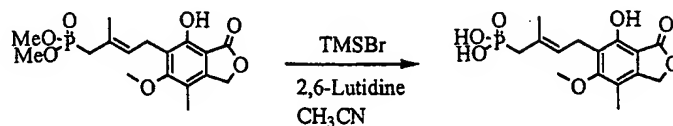
[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyl]-phosphonic acid dimethyl ester

A solution of 6-(4-bromo-3-methyl-but-2-enyl)-7-hydroxy-5-methoxy-4-methyl-3H-isobenzofuran-1-one (33 mg, 0.097 mmol) in trimethylphosphite (1.0 mL, 8.5 mmol) was heated to 100 °C for 1 hour, whereupon complete reaction was indicated by LCMS. The reaction was worked up by removal of the excess reagent under reduced pressure and the residue was purified by silica gel chromatography using EtOAc-hexanes (20-100%) to provide 20 mg (60%) of the desired product. ^1H NMR (300 MHz, CDCl_3) δ 1.90 (s, 3H), 2.09 (s, 3H), 2.48 (d, 2H, $J = 22$ Hz), 3.38 (t, 2H, $J = 6$ Hz), 3.64 (d, 6H, $J = 11$ Hz), 3.72 (s, 3H), 5.14 (s, 2H), 5.33 (q, 1H, $J = 6$ Hz), 7.65 (br s, 1H) ppm; MS (m/z) 371 $[\text{M}+\text{H}]^+$.

25

Example 257: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.



5

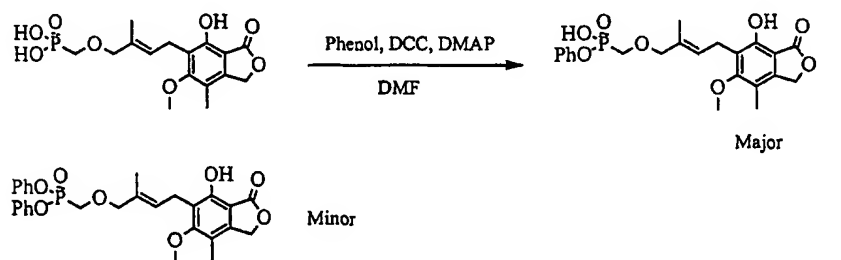
[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyl]-phosphonic acid

To a solution of [4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyl]-phosphonic acid dimethyl ester (18 mg, 0.049 mmol) in acetonitrile (2 mL) was added TMSBr (63 μ L, 0.49 mmol) and 2,6-lutidine (85 μ L, 0.73 mmol) at 0°C. The reaction solution was allowed to warm to room temperature and stirred for 2 hours when completion of the reaction was observed by LCMS. The reaction was cooled to 0°C and quenched by the addition of MeOH. The reaction mixture was concentrated under reduced pressure and the residue was purified by RP HPLC using a C18 column with a gradient of H₂O-acetonitrile (5-0%) over 20 minutes to provide 12.2 mg (73%) of the product. ¹H NMR (300 MHz, CD₃OD) δ 1.95 (s, 3H), 2.15 (s, 3H), 2.48 (d, 2H, *J* = 22 Hz), 3.44 (t, 2H, *J* = 6 Hz), 3.79 (s, 3H), 5.24 (s, 2H), 5.38 (q, 1H, *J* = 7 Hz), 6.87 (br s, 1H) ppm; MS (*m/z*) 341 [M-H]⁻.

20

Example 258: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.



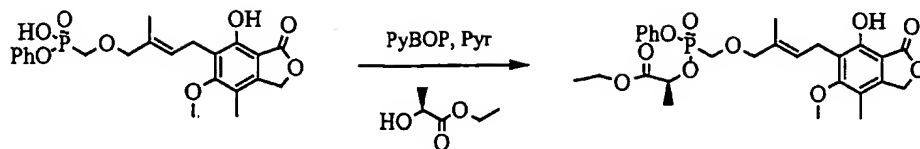
25

[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid monophenyl ester and [4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid diphenyl ester

- 5 To a solution of [4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid (49 mg, 0.13 mmol) in DMF (0.4 mL) and phenol (62 mg, 0.65 mmol) was added dicyclohexyl carbodiimide (107 mg, 0.52 mmol) and DMAP (8 mg, 0.065 mmol) in DMF (0.6 mL), slowly at 0°C. The reaction was allowed to warm to
- 10 room temperature and heated to 140°C for 10 hours. After cooling to room temperature the mixture was filtered and extracted with aqueous 1N NaOH solution. The aqueous layer was acidified with aqueous 1N HCl and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated to dryness. The residue was purified by RP HPLC to provide 18.5 mg of [4-(4-
- 15 hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid monophenyl ester (major product, Example 8) as a pale yellow solid and 4.1 mg of [4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid diphenyl ester (minor product) also as a pale yellow solid.
- 20 Major product: ¹H NMR (300 MHz, CD₃OD) δ 1.82 (s, 3H), 2.16 (s, 3H), 3.46 (d, 2H, *J* = 7 Hz), 3.70 (d, 2H, *J* = 8 Hz), 3.77 (s, 3H), 3.96 (s, 2H), 5.25 (s, 2H), 5.52 (t, 1H, *J* = 8 Hz), 7.10- 7.21 (m, 3H), 7.30 (t, 2H, *J* = 8 Hz) ppm; ³¹P (121.4 MHz, CD₃OD) δ 17.3 ppm; MS (*m/z*) 449.0 [M+H]⁺, 471.2 [M+Na]⁺. Minor product: ¹H NMR (300 MHz, CD₃OD) δ 1.82 (s, 3H), 2.15 (s, 3H), 3.47 (d, 2H,
- 25 *J* = 7 Hz), 3.77 (s, 3H), 3.98- 4.06 (m, 4H), 5.25 (s, 2H), 5.50- 5.61 (m, 1H), 7.10- 7.25 (m, 6H), 7.30- 7.41 (m, 4H) ppm; ³¹P (121.4 MHz, CD₃OD) δ 16.3 ppm; MS (*m/z*) 525.2 [M+H]⁺, 547.2 [M+Na]⁺.

Example 259: Preparation of Representative Compounds of the Invention.

- 30 Representative compounds of the invention can be prepared as illustrated below.

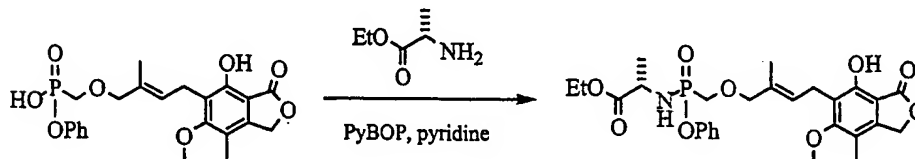


2-[[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phenoxy-phosphinoyloxy}-propionic acid ethyl ester

To a solution of [4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid monophenyl ester (18.5 mg, 0.040 mmol) and ethyl (S)-(-)-lactate (47 μ L, 0.400 mmol) in pyridine (0.5 mL) was added PyBOP (32 mg, 0.060 mmol). The solution was stirred at room temperature for 1 hour, when an additional portion of PyBOP (21 mg, 0.040 mmol) was added. The solution was stirred for another hour and concentrated. The residue was purified by HPLC to provide 7.5 mg of the desired product as a clear oil. ^1H NMR (300 MHz, CD_3OD) δ 1.22 and 1.25 (t, 3H, $J=7$ Hz), 1.42 and 1.50 (d, 3H, $J=7$ Hz), 1.82 and 1.83 (s, 3H), 2.16 (s, 3H), 3.47 (d, 2H, $J=7$ Hz), 3.78 (s, 3H), 3.89 (d, 1H, $J=8$ Hz), 3.93-4.02 (m, 3H), 4.10-4.22 (m, 2H), 4.94-5.08 (m, 1H), 5.25 (s, 2H), 5.50-5.60 (m, 1H), 7.15-7.27 (m, 3H), 7.33-7.41 (m, 2H) ppm; ^{31}P (121.4 MHz, CD_3OD) δ 18.9, 20.3 ppm (diastereomers at phosphorus); MS (m/z) 549.2 $[\text{M}+\text{H}]^+$, 571.3 $[\text{M}+\text{Na}]^+$.

Example 260: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.

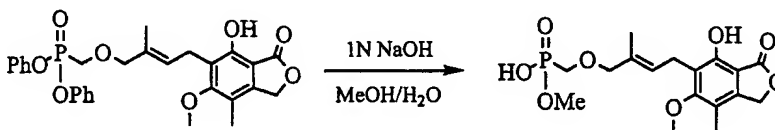


2-[[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phenoxy-phosphinoylamino}-propionic acid ethyl ester

To a solution of [4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid monophenyl ester (20 mg, 0.045 mmol) and L-alanine ethyl ester hydrochloride (68.5mg, 0.45mmol) in pyridine (1.0 mL) was added PyBOP (70mg, 0.14mmol). After stirring overnight, the mixture was concentrated and the residue purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 3.6 mg of the product as a colorless gel. ¹H NMR (300 MHz, CD₃OD) δ 1.17-1.3 (m, 6H), 1.8-1.9 (m, 3H), 2.16 (s, 3H), 3.17 (m, 1H), 3.47 (d, 2H), 3.72-3.8 (m, 5H), 3.92-4.2 (m, 4H), 5.25 (s, 2H), 5.54 (m, 1H), 7.18 (m, 3H), 7.33 (m, 2H) ppm; ³¹P (121.4 MHz, CD₃OD) δ 24.1, 25.0 ppm (diastereomers at phosphorus); MS (*m/z*) 546.2 [M-H]⁺.

Example 261: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.



[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid monomethyl ester

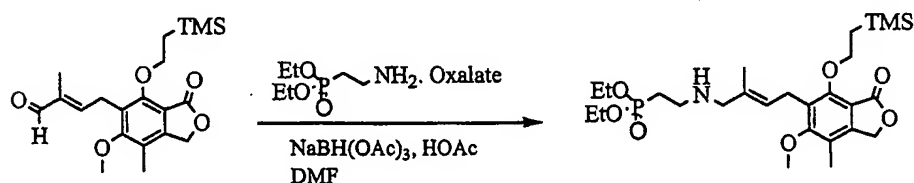
To a solution of [4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid diphenyl ester (53 mg, 0.1 mmol) in methanol (0.5 mL) was added an aqueous solution of 1N NaOH (300 μL). After stirring overnight, the mixture was concentrated and the residue purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 5 mg of the product as a colorless gel, together with the phosphonic acid monophenyl ester (7mg) and the

phosphonic acid dimethyl ester (14.5mg). ^1H NMR (300 MHz, CD_3OD) δ 1.84 (s, 3H), 2.16 (s, 3H), 3.47 (d, 2H, $J=7$ Hz), 3.6 (d, 2H, $J=12$ Hz), 3.75 (d, 3H, $J=11$ Hz), 3.79 (s, 3H), 3.94 (s, 2H), 5.26 (s, 2H), 5.53 (t, 1H, $J=7$ Hz) ppm; ^{31}P (121.4 MHz, CD_3OD) δ 21.5 ppm; MS (m/z) 385.2 $[\text{M}-\text{H}]^+$, 387.1 $[\text{M}+\text{H}]^+$.

5

Example 262: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.

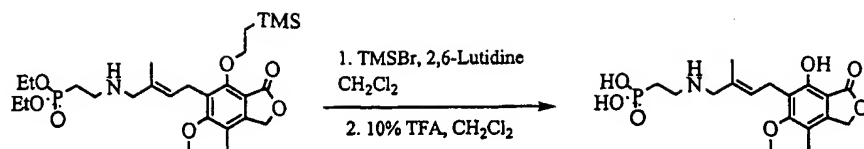


10

(2-{4-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino}-ethyl)-phosphonic acid diethyl ester

To a solution of 4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enal (84 mg, 0.22 mmol), (2-amino-ethyl)-phosphonic acid diethyl ester oxalate (91 mg, 0.33 mmol), and sodium triacetoxyborohydride (93 mg, 0.44 mmol) in DMF (1.5 mL) was added acetic acid (60 μL , 1.0 mmol) at room temperature. The solution was stirred for 2 days when it was quenched by addition of saturated aqueous sodium bicarbonate solution and EtOAc . The organic layer was separated and concentrated under reduced pressure. The residue was purified by RP HPLC using a C18 column with a gradient of H_2O , 0.1% TFA-acetonitrile, 0.1% TFA to provide 115 mg (96%) of the product as an oil. ^1H NMR (300 MHz, CDCl_3) δ 0.04 (s, 9H), 1.16- 1.27 (m, 2H), 1.34 (t, 6H, $J=7$ Hz), 1.94 (s, 3H), 2.18 (s, 3H), 2.20- 2.31 (m, 2H), 3.13- 3.31 (m, 2H), 3.48 (d, 2H, $J=7$ Hz), 3.54 (s, 2H), 3.78 (s, 3H), 4.14 (pent, 4H, $J=7$ Hz), 4.30- 4.37 (m, 2H), 5.13 (s, 2H), 5.65 (t, 1H, $J=7$ Hz), 6.23 (br s, 2H) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 27.8 ppm; MS (m/z) 542.3 $[\text{M}+\text{H}]^+$, 564.2 $[\text{M}+\text{Na}]^+$.

25



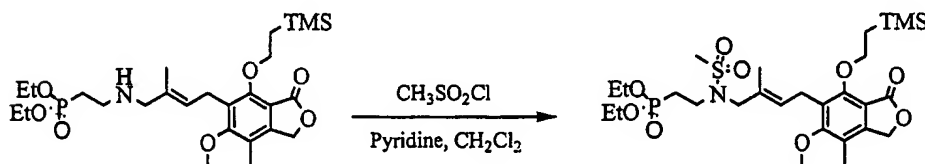
{2-[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enylamino]-ethyl}-phosphonic acid

- 5 A solution of (2-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilanylethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino}-ethyl)-phosphonic acid diethyl ester (30 mg, 0.055 mmol), TMSBr (72 μ L, 0.55 mmol), and 2,6-lutidine (64 μ L, 0.55 mmol) was stirred in CH_2Cl_2 (1 mL) and DMF (0.5 mL) for 1 hour at ambient temperature. The reaction mixture was purified by RP
- 10 HPLC using a C18 column with a gradient of H_2O , 0.1% TFA-acetonitrile, 0.1% TFA to provide 7.8 mg of the product as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 1.96 (s, 3H), 1.95- 2.07 (m, 2H), 2.16 (s, 3H), 3.10-3.24 (m, 2H), 3.51 (d, 2H, $J=7$ Hz), 3.57 (s, 2H), 3.81 (s, 3H), 5.25 (s, 2H), 5.73 (t, 1H, $J=7$ Hz) ppm; ^{31}P (121.4 MHz, CD_3OD) δ 20.2 ppm; ^{19}F NMR (282.6 MHz, CD_3OD) δ -74.0 ppm; MS (m/z) 386.3 $[\text{M}+\text{H}]^+$.
- 15

Example 263: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.

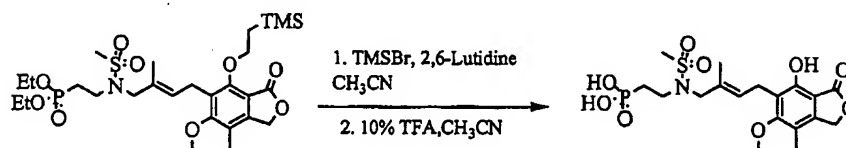
20



- [2-(Methanesulfonyl-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilanylethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-amino)-ethyl]-phosphonic acid diethyl ester**
- 25

A solution of (2-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilanylethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino}-ethyl)-

- phosphonic acid diethyl ester (45 mg, 0.092 mmol) in CH_2Cl_2 (0.5 mL) was stirred with methanesulfonyl chloride (21 μL , 0.28 mmol) and pyridine (45 μL , 0.55 mmol) at ambient temperature overnight. The reaction was quenched by addition of 2 drops of water. The reaction mixture was concentrated and purified
- 5 by RP HPLC using a C18 column with a gradient of H_2O , 0.1% TFA-acetonitrile, 0.1% TFA to provide 36 mg of the product (63%) as a clear gel. ^1H NMR (300 MHz, CDCl_3) δ 0.05 (s, 9H), 1.18- 1.29 (m, 2H), 1.29 (t, 6H, $J=7$ Hz), 1.85 (s, 3H), 2.00- 2.13 (m, 2H), 2.19 (s, 3H), 2.85 (s, 3H), 3.32- 3.43 (m, 2H), 3.47 (d, 2H, $J=7$ Hz), 3.69 (s, 2H), 3.79 (s, 3H), 4.05 (pent, 4H, $J=7$ Hz),
- 10 4.30- 4.37 (m, 2H), 5.13 (s, 2H), 5.45 (t, 1H, $J=7$ Hz) ppm; ^{31}P (121.4 MHz, CD_3Cl) δ 27.5 ppm; MS (m/z) 642.2 $[\text{M}+\text{Na}]^+$.

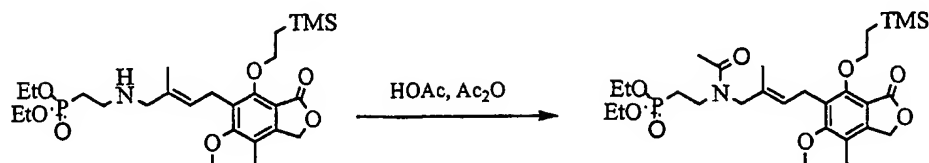


- 15 (2-{{4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyl}-methanesulfonyl-amino}-ethyl)-phosphonic acid

- A solution of [2-(methanesulfonyl-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-amino)-ethyl]-phosphonic acid diethyl ester (18 mg, 0.029 mmol) in acetonitrile
- 20 (0.5 mL) was stirred with TMSBr (38 μL , 0.29 mmol) and 2,6-lutidine (34 μL , 0.29 mmol) for 2 hours at room temperature. The reaction was worked up by addition of EtOAc and aqueous 1N HCl. The organic layer was washed with brine and the solvent was removed *in vacuo*. The residue was suspended in a solution of 10% TFA- CH_2Cl_2 for 10 minutes before it was dried to provide 9.9
- 25 mg of the desired product (73%) as a white solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.76 (s, 3H), 1.76- 1.88 (m, 2H), 2.10 (s, 3H), 2.87 (s, 3H), 3.24- 3.35 (m, 2H), 3.39 (d, 2H, $J=7$ Hz), 3.65 (s, 2H), 3.75 (s, 3H), 5.22 (s, 2H), 5.41- 5.48 (m, 1H) ppm; ^{31}P (121.4 MHz, $\text{DMSO}-d_6$) δ 21.4 ppm; MS (m/z) 464.1 $[\text{M}+\text{H}]^+$.

- 30 **Example 264: Preparation of Representative Compounds of the Invention.**

Representative compounds of the invention can be prepared as illustrated below.

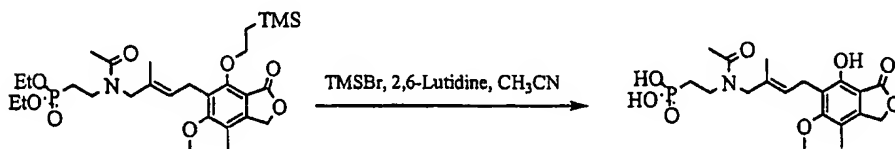


5

[2-(Acetyl-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-amino)-ethyl]-phosphonic acid diethyl ester

To a solution of (2-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino}-ethyl)-phosphonic acid diethyl ester (32 mg, 0.059 mmol) in acetic acid (0.5 mL) was added acetic anhydride (0.5 mL). The solution was stirred at room temperature for 90 minutes when it was quenched by addition of 2 drops of water. The solution was dried *in vacuo* and the residue was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 28 mg of the product (81%) as a clear gel. The NMR data of this compound shows two rotamers in a ratio of 70:30. ¹H NMR (300 MHz, CDCl₃) δ 0.05 (s, 9H), 1.17- 1.27 (m, 2H), 1.30 and 1.31 (t, 6H, *J*= 7 Hz), 1.70-1.79 (m, 2H), 1.76 (s, 3H), 2.00 (s, 3H), 2.18 (s, 3H), 3.40- 3.52 (m, 2H), 3.46 (d, 2H, *J*= 7 Hz), 3.77 (s, 3H), 3.79 and 3.93 (s, 3H), 4.07 (pent, 4H, *J*= 7 Hz), 4.27- 4.35 (m, 2H), 5.13 (s, 2H), 5.22- 5.30 (m, 1H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 27.5 and 28.9 ppm; MS (*m/z*) 584.1 [M+H]⁺, 606.2 [M+Na]⁺.

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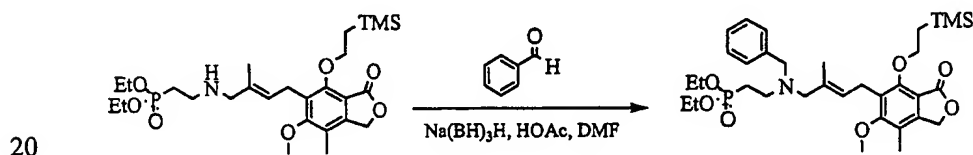
25

(2-{Acetyl-[4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyl]-amino}-ethyl)-phosphonic acid

To a solution of [2-(acetyl-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-amino)-ethyl]-phosphonic acid diethyl ester (14 mg, 0.024 mmol) in acetonitrile (0.5 mL) was added TMSBr (31 μ L, 0.24 mmol) and 2,6-lutidine (28 μ L, 0.24 mmol). The solution was stirred at room temperature for 1 hour. The reaction was quenched by addition of methanol and aqueous 1N HCl. The product was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The product was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 5.4 mg of the product (53%) as a white solid. The NMR data of this compound shows two rotamers. ¹H NMR (300 MHz, CDCl₃) δ 1.67 and 1.73 (s, 3H), 1.85-2.12 (m, 5H), 2.13 (s, 3H), 3.30-3.61 (m, 4H), 3.75 (s, 3H), 3.76 (br s, 2H), 5.17 (s, 2H), 5.31 (br s, 1H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 27.5 and 28.8 ppm; MS (*m/z*) 428.2 [M+H]⁺, 450.2 [M+Na]⁺.

Example 265: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.

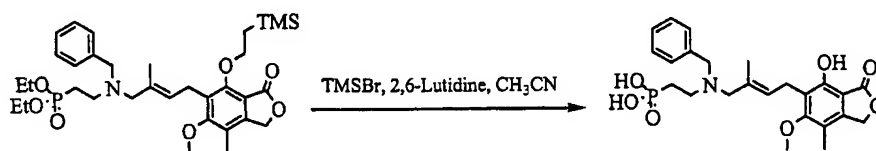


[2-(Benzyl-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-amino)-ethyl]-phosphonic acid diethyl ester

A solution of (2-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino}-ethyl)-phosphonic acid diethyl ester (30 mg, 0.055 mmol), benzaldehyde (5.6 μ L, 0.055 mmol), and sodium triacetoxyborohydride (23 mg, 0.11 mmol) was stirred with acetic acid (15.7 μ L, 0.28 mmol) in DMF (0.5 mL) at room temperature overnight. The reaction was quenched with a 10% aqueous Na₂CO₃ solution and the

product was extracted with EtOAc. The organic layer was dried and concentrated under reduced pressure. The product was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 15 mg of the product (43%) as a clear gel. ¹H NMR (300 MHz, CDCl₃) δ 0.02 (s, 9H), 1.18- 1.25 (m, 2H), 1.24 (t, 6H, *J*= 7 Hz), 1.86 (s, 3H), 1.88- 2.02 (m, 2H), 2.16 (s, 3H), 2.65- 2.74 (m, 2H), 3.93 (s, 2H), 3.46 (br d, 4H, *J*= 7 Hz), 3.76 (s, 3H), 4.00 (pent, 4H, *J*= 7 Hz), 4.25- 4.34 (m, 2H), 5.11 (s, 2H), 5.34- 5.43 (m, 1H), 7.18- 7.33 (m, 5H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 30.9 ppm; MS (*m/z*) 632.4 [M+H]⁺, 654.3 [M+Na]⁺.

10

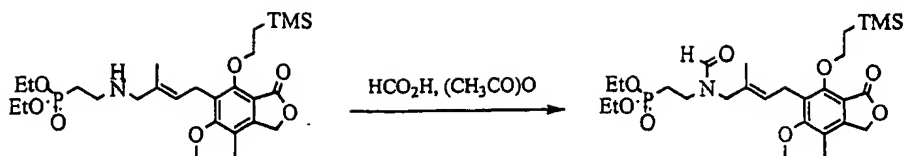


(2-{Benzyl-[4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyl]-amino}-ethyl)-phosphonic acid

A solution of (2-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino}-ethyl)-phosphonic acid diethyl ester (15 mg, 0.024 mmol) in acetonitrile (0.5 mL) was treated with TMSBr (31 μL, 0.24 mmol) and 2,6-lutidine (28 μL, 0.24 mmol). The solution was stirred at ambient temperature for 1 hour, when it was quenched with methanol. The solvent was removed under reduced pressure and the residue was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 11 mg of the product (93%) as a white solid. ¹H NMR (300 MHz, CD₃OD) δ 1.89 (s, 3H), 2.03- 2.15 (m, 2H), 2.14 (s, 3H), 3.30- 3.47 (m, 2H), 3.50 (br s, 2H), 3.62 (br s, 2H), 3.79 (s, 3H), 4.28 (s, 2H), 5.23 (s, 2H), 5.76 (br s, 1H), 7.46 (br s, 5H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 20.1 ppm; MS (*m/z*) 476.3 [M+H]⁺, 498.3 [M+Na]⁺.

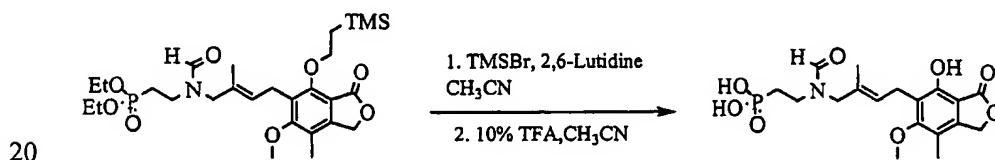
Example 266: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.



[2-(Formyl-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-amino)-ethyl]-phosphonic acid diethyl ester

To a solution of (2-{4-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino}-ethyl)-phosphonic acid diethyl ester (74 mg, 0.14 mmol) in formic acid (1 mL) was added formic anhydride (1 mL) and the solution was stirred at room temperature for 1 hour. The reaction mixture was concentrated and the crude product carried onto the next step. The NMR data of this compound shows two rotamers with the ratio of 70:30. ¹H NMR (300 MHz, CDCl₃) δ 0.05 (s, 9H), 1.18- 1.28 (m, 2H), 1.28 and 1.30 (t, 6H, *J* = 7 Hz), 1.74 (s, 3H), 1.84- 2.08 (m, 2H), 2.19 (s, 3H), 3.34- 3.45 (m, 2H), 3.47 (d, 2H, *J* = 7 Hz), 3.72 and 3.87 (s, 2H), 3.78 and 3.79 (s, 3H), 4.06 and 4.07 (pent, 4H, *J* = 7 Hz), 4.26- 4.37 (m, 2H), 5.13 (s, 2H), 5.30-5.46 (m, 1H), 8.03 and 8.19 (s, 1H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 27.5 and 28.1 ppm; MS (*m/z*) 570.1 [M+H]⁺, 592.2 [M+Na]⁺.



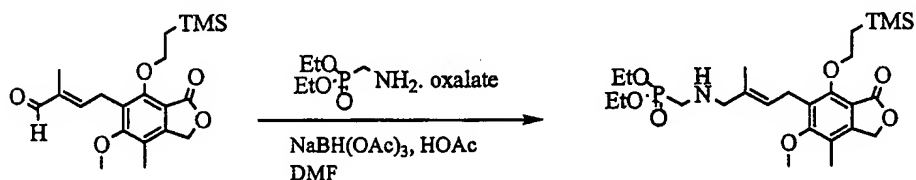
(2-{Formyl-[4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyl]-amino}-ethyl)-phosphonic acid

To a solution of crude [2-(formyl-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-amino)-ethyl]-phosphonic acid diethyl ester (78 mg, 0.14 mmol) in acetonitrile (1 mL) was added TMSBr (177 μL, 1.4 mmol) and 2,6-lutidine (163 μL, 1.4 mmol). The solution was stirred at room temperature for 1 hour when it was

quenched by addition of methanol and 1N aqueous HCl. The product was extracted with EtOAc and purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 29 mg of the product as a white solid. The NMR data of this compound shows two rotamers
 5 with the ratio of approximately 70:30. ¹H NMR (300 MHz, CD₃OD) δ 1.62 and 1.64 (s, 3H), 1.83- 1.98 (m, 2H), 2.16 (s, 3H), 3.38- 3.55 (m, 4H), 3.78 (s, 3H), 3.80 and 3.91 (s, 2H), 5.22 (s, 2H), 5.39- 5.52 (m, 1H), 8.03 and 8.18 (s, 1H) ppm; MS (*m/z*) 414.2 [M+H]⁺, 436.2 [M+Na]⁺.

10 Example 267: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.

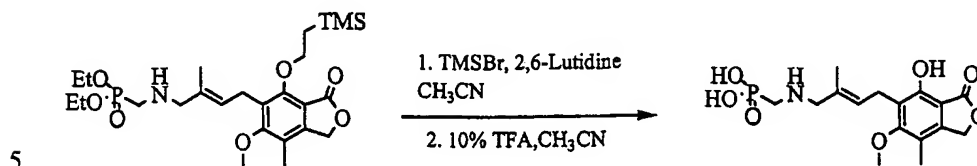


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(({4-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino}-methyl)-phosphonic acid diethyl ester

To a solution of 4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enal (500 mg, 1.33 mmol), (2-aminomethyl)phosphonic acid diethyl ester oxalate (376 mg, 1.46 mmol), sodium triacetoxyborohydride (563 mg, 2.66 mmol) in DMF (10 mL) was added acetic acid (380 μL, 6.65 mmol) at room temperature. The solution was stirred overnight when it was quenched by addition of saturated aqueous
 25 sodium bicarbonate solution and EtOAc. The organic layer was separated and concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 500 mg (71%) of the product as an oil. ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 9H), 1.13- 1.23 (m, 2H), 1.25 and 1.27 (t, 6H, *J*= 7 Hz), 1.65- 1.75 (m, 2H), 1.77 (s, 3H), 2.13 (s, 3H), 2.80 (s, 1H), 3.14 (s, 2H),

3.41 (d, 2H, $J = 7$ Hz), 3.73 (s, 3H), 4.08 and 4.09 (pent, 4H, $J = 7$ Hz), 4.20-4.30 (m, 2H), 5.08 (s, 2H), 5.30 (t, 1H, $J = 7$ Hz) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 26.5 ppm; MS (m/z) 528.1 $[\text{M}+\text{H}]^+$, 550.2 $[\text{M}+\text{Na}]^+$.



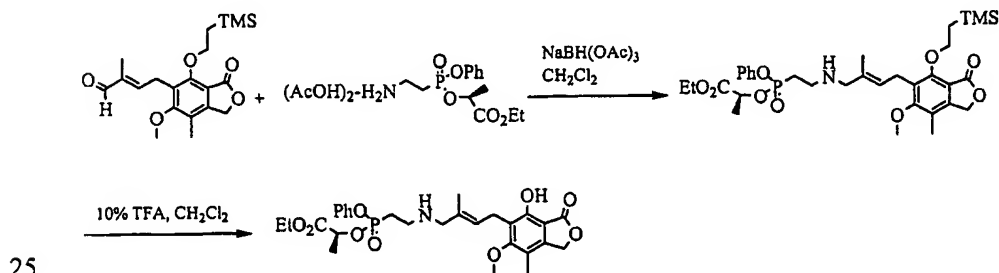
{[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enylamino]-methyl}-phosphonic acid

To a solution of ([4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino]-methyl)-phosphonic acid diethyl ester (20 mg, 0.038 mmol) in DMF (0.5 mL) was added TMSBr (49 μL , 0.38 mmol) and 2,6-lutidine (44 μL , 0.38 mmol). The solution was stirred at room temperature for 1 hour when it was quenched by addition of methanol. The product was purified by RP HPLC using a C18 column with a
 15 gradient of H_2O , 0.1% TFA-acetonitrile, 0.1% TFA to provide 5.6 mg of the product as a white solid. ^1H NMR (300 MHz, CD_3OD and CDCl_3) δ 1.93 (s, 3H), 2.13 (s, 3H), 2.94 (br d, 2H, $J = 11$ Hz), 3.42-3.53 (m, 2H), 3.60 (s, 2H), 3.78 (s, 3H), 5.22 (s, 2H), 5.71 (br s, 1H) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 8.5 ppm; MS (m/z) 372.2 $[\text{M}+\text{H}]^+$, 743.2 $[\text{2M}+\text{H}]^+$.

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Example 268: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.

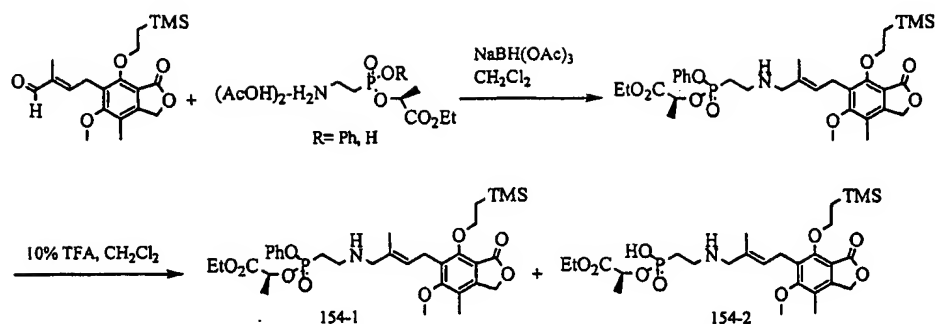


2-({2-[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enylamino]-ethyl}-phenoxy-phosphinoyloxy)-propionic acid ethyl ester

A solution of 4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enal (188 mg, 0.5 mmol) was stirred with 2-[(2-aminoethyl)phenoxy-phosphinoyloxy]-propionic acid ethyl ester acetic acid salt (315.8 mg, 0.75 mmol) in CH₂Cl₂ (3 mL) for 2 hours at ambient temperature. Sodium triacetoxyborohydride (159 mg, 0.75 mmol) was added to the solution and the reaction was allowed to proceed for 1 hour. The reaction was quenched by addition of a saturated aqueous solution of NaHCO₃ and the product was extracted with EtOAc. The organic layer was removed under reduced pressure and the residue was resuspended in a 10% TFA/ CH₂Cl₂ for 1 hour. The reaction mixture was concentrated and the product was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 198 mg of the product as a white solid. The NMR data of this compound shows two diastereomers at phosphorus in a ratio of approximately 45: 55. ¹H NMR (300 MHz, CD₃OD) δ 1.23 and 1.24 (t, 3H, *J* = 7 Hz), 1.38 and 1.52 (d, 3H, *J* = 7 Hz), 1.97 and 1.98 (s, 3H), 2.14 (s, 3H), 2.44- 2.66 (m, 2H), 3.31- 3.48 (m, 2H), 3.51 (d, 2H, *J* = 7 Hz), 3.66 (d, 2H, *J* = 5 Hz), 3.80 (s, 3H), 4.10- 4.27 (m, 2H), 4.90- 5.10 (m, 1H), 5.20 (s, 2H), 5.73- 5.82 (m, 1H), 7.15- 7.27 (m, 3H), 7.35- 7.45 (m, 2H) ppm; ³¹P (121.4 MHz, CD₃OD) δ 22.6, 24.3 ppm; MS (*m/z*) 561.9 [M+H]⁺.

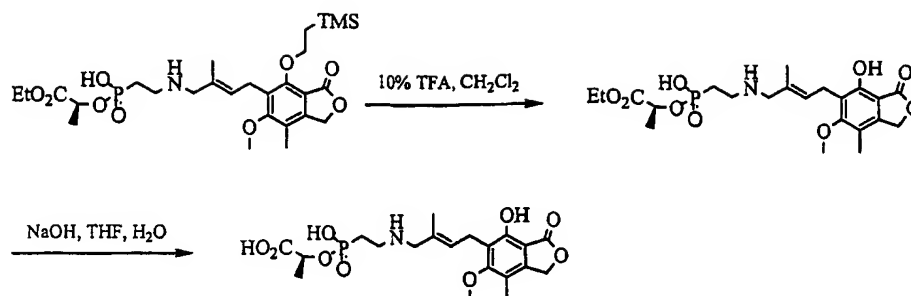
Example 269: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.



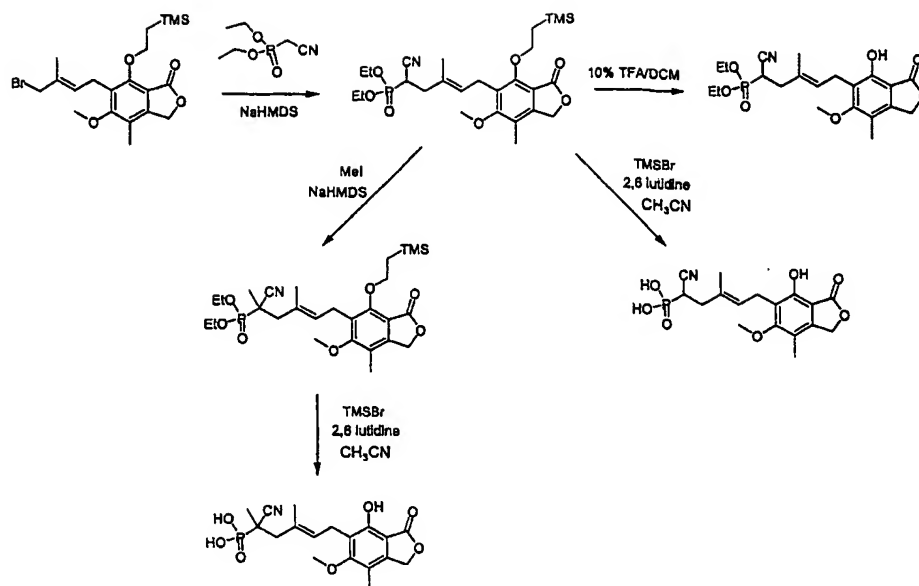
2-[Hydroxy-(2-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino}-ethyl)-phosphinoyloxy]-propionic acid ethyl ester

- 5 A solution of 4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enal (38 mg, 0.1 mmol) was stirred with 2-[(2-aminoethyl)-phenoxy-phosphinoyloxy]-propionic acid ethyl ester acetic acid (63 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) for 2 hours at ambient temperature. Sodium triacetoxyborohydride (32 mg, 0.15 mmol) was
- 10 added to the solution and the reaction was allowed to proceed for 1 hour. The reaction was quenched by addition of a saturated aqueous solution of NaHCO_3 and the product was extracted with EtOAc. The organic layer was removed under reduced pressure and the residue was re-suspended in 10% TFA/ CH_2Cl_2 for 1 hour. The reaction mixture was concentrated and the product was purified
- 15 by RP HPLC using a C18 column with a gradient of H_2O , 0.1% TFA-acetonitrile, 0.1% TFA to provide 15 mg of the product (154-2). ^1H NMR (300 MHz, CDCl_3) δ 0.04 (s, 9H), 1.15- 1.24 (m, 2H), 1.26 (t, 3H, $J = 7$ Hz), 1.48 (d, 3H, $J = 7$ Hz), 1.93 (s, 3H), 2.10- 2.25 (m, 2H), 2.18 (s, 3H), 3.10- 3.31 (m, 2H), 3.48 (d, 2H, $J = 7$ Hz), 3.48- 3.61 (m, 2H), 3.77 (s, 3H), 4.04- 4.21 (m, 2H), 4.29-
- 20 4.40 (m, 2H), 4.81- 4.92 (m, 1H), 5.13 (s, 2H), 5.64 (t, 1H, $J = 7$ Hz), 8.70- 9.11 (m, 3H) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 21.9 ppm; MS (m/z) 586.3 $[\text{M}+\text{H}]^+$, 1171.4 $[\text{2M}+\text{H}]^+$.



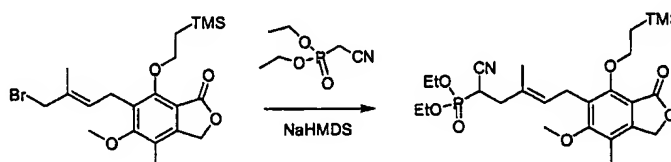
2-(Hydroxy-{2-[4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enylamino]-ethyl}-phosphinoyloxy)-propionic acid

A solution of 2-[hydroxy-(2-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino}-ethyl)-phosphinoyloxy]-propionic acid ethyl ester (15 mg, 0.026 mmol) in 10% TFA-CH₂Cl₂ (1 mL) was stirred at ambient temperature for 10 minutes. The reaction was worked up by removal of the solvent. The residue was dissolved in THF (0.5 mL) and water (0.4 mL) and 1N aqueous NaOH solution (0.1 mL) was added. The solution was stirred at room temperature for 20 minutes when it was acidified with 1N aqueous HCl solution. The resulting solution was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 6.8 mg of the product as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 1.38 (d, 3H, *J* = 7 Hz), 1.91 (s, 3H), 2.13 (s, 3H), 2.12-2.28 (m, 2H), 3.12-3.33 (m, 2H), 3.41 (d, 2H, *J* = 6 Hz), 3.56 (br s, 2H), 3.75 (s, 3H), 4.71-4.88 (m, 1H), 5.16 (s, 2H), 5.58-5.71 (m, 1H), 7.88 (br s, 3H), 8.60 (br s, 1H), 8.78 (br s, 1H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 22.0 ppm; MS (*m/z*) 458.3 [M+H]⁺, 480.3 [M+Na]⁺.



Example 270: Preparation of Representative Compounds of the Invention.

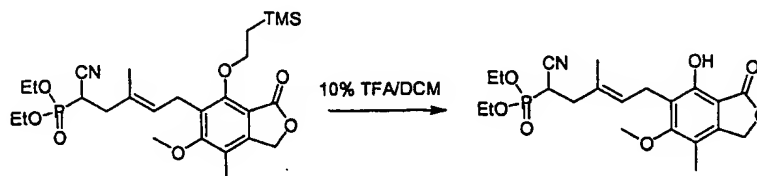
Representative compounds of the invention can be prepared as illustrated
 5 below.



10 {1-Cyano-5-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-3-methyl-pent-3-enyl}-phosphonic acid diethyl ester

To a solution of diethyl cyanomethylphosphonate (241 mg, 1.38 mmol) in THF (1 mL) was added a THF solution of sodium bis(trimethylsilyl)amide (1.0 M, 1.13 mL, 1.15 mmol). After stirring for 30 minutes, the solution was added
 15 dropwise to a solution of 6-(4-bromo-3-methyl-but-2-enyl)-7-hydroxy-5-methoxy-4-methyl-3H-isobenzofuran-1-one (100 mg, 0.23 mmol) in THF (1 mL). The resulting mixture was allowed to stir at room temperature for one hour before saturated aqueous ammonium chloride was added. The reaction mixture was extracted with ethyl acetate. The organic layer was dried over sodium

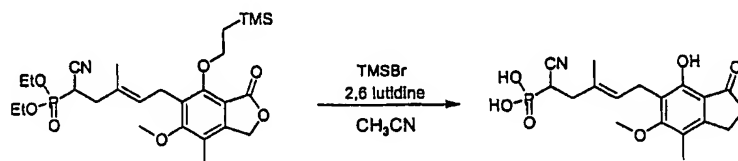
sulfate and concentrated to dryness. The residue was purified by silica gel column chromatography, affording 110 mg (90 %) of the desired product. ^1H NMR (300 MHz, CDCl_3) δ 0.04 (s, 9H), 1.24 (dd, $J = 7, 8$ Hz, 2H), 1.36 (t, 6H), 1.86 (s, 3H), 2.17 (s, 3H), 2.43-2.57 (m, 2H), 3.04-3.17 (m, 1H), 3.47 (d, $J = 7.2$ Hz, 2H), 3.79 (s, 3H), 4.12-4.37 (m, 6H), 5.13 (s, 2H), 5.44 (t, $J = 7.2$ Hz, 1H) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 18.18 ppm; MS (m/z) 560 $[\text{M}+\text{Na}]^+$.



- 10 **[1-Cyano-5-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-pent-3-enyl]-phosphonic acid diethyl ester**
 {1-Cyano-5-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-3-methyl-pent-3-enyl}-phosphonic acid diethyl ester (25mg, 0.047 mmol) was dissolved in a solution of 10% TFA/ CH_2Cl_2 (5 mL) and stirred at room temperature for 2 hours. The reaction mixture was dried under reduced pressure and the product was purified by RP-HPLC to provide 16 mg (80%) of the desired product as a white solid. ^1H NMR (300 MHz, CDCl_3) δ 1.38 (t, 6H), 1.86 (s, 3H), 2.15 (s, 3H), 2.40-2.58 (m, 2H), 3.01-3.14 (m, 1H), 3.45 (d, $J = 7.2$ Hz, 2H), 3.79 (s, 3H), 4.18-4.30 (m, 4H), 5.21 (s, 2H), 5.48 (t, $J = 7.2$ Hz, 1H) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 18.09 ppm; MS (m/z) 436 $[\text{M}-\text{H}]^-$, 438 $[\text{M}+\text{H}]^+$.

Example 271: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.

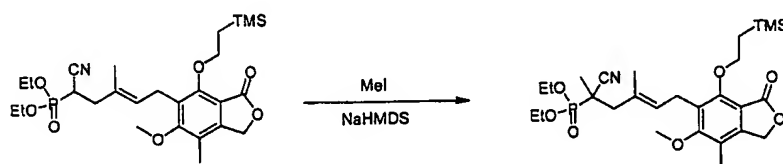


[1-Cyano-5-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-3-methyl-pent-3-enyl]-phosphonic acid

To a solution of {1-cyano-5-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-3-methyl-pent-3-enyl}-phosphonic acid diethyl ester (35 mg, 0.065 mmol) in acetonitrile (2 mL) was added TMSBr (180 μ L, 1.38 mmol) and 2,6-lutidine (160 μ L, 1.38 mmol). The reaction solution was allowed stir at room temperature for one hour before quenching with MeOH. The reaction mixture was dried under reduced pressure and the residue was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 15 mg (60 %) of the desired product. ¹H NMR (300 MHz, CD₃OD) δ 1.86 (s, 3H), 2.15 (s, 3H), 2.38-2.57 (m, 2H), 3.17-3.28 (m, 1H), 3.44 (d, J = 7.2 Hz, 2H), 3.80 (s, 3H), 5.25 (s, 2H), 5.47 (t, J = 7.2 Hz, 1H) ppm; ³¹P (121.4 MHz, CD₃OD) δ 15.28 ppm; MS (m/z) 380 [M-H]⁻, 382 [M+H]⁺.

Example 272: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.

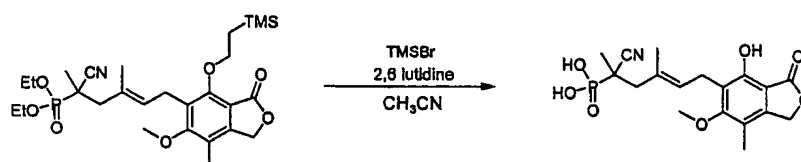


{1-Cyano-5-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-1,3-dimethyl-pent-3-enyl}-phosphonic acid

diethyl ester

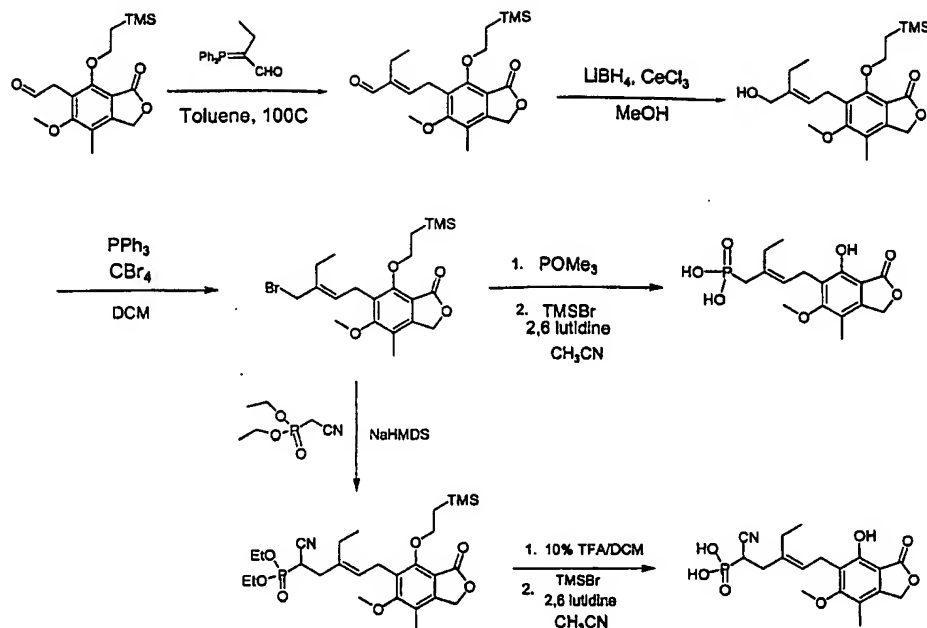
To a solution of {1-cyano-5-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-3-methyl-pent-3-enyl}-phosphonic acid diethyl ester (45 mg, 0.084 mmol) in THF (0.5 mL) was added sodium bis(trimethylsilyl)amide (1.0 M, 1.13 mL, 1.15 mmol). After stirring for 20 minutes, iodomethane (52 μ L, 0.84 mmol) was added dropwise

and the resulting mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated to dryness. The residue was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to afford 6.6 mg (23 %) of the desired product. ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 9H), 1.16 (dd, J = 7, 8 Hz, 2H), 1.31 (t, 6H), 1.38 (d, 3H), 1.92 (s, 3H), 2.17 (s, 3H), 2.23 (m, 1H), 2.65 (m, 1H), 3.30-3.42 (m, 2H), 3.73 (s, 3H), 4.14-4.27 (m, 6H), 5.08 (s, 2H), 5.28 (t, J = 7.2 Hz, 1H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 22.26 ppm; MS (*m/z*) 574 [M+Na]⁺.



[1-Cyano-5-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-1,3-dimethyl-pent-3-enyl]-phosphonic acid

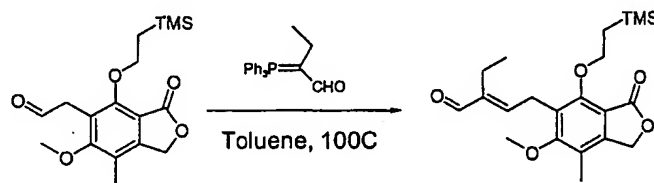
To a solution of {1-cyano-5-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-1,3-dimethyl-pent-3-enyl}-phosphonic acid diethyl ester (18 mg, 0.04 mmol) in DMF (0.5 mL) and DCM (0.5 mL) was added TMSBr (51 μL, 0.4 mmol) and 2,6-lutidine (46 μL, 0.4 mmol). The reaction solution was allowed stir at room temperature overnight before quenching with MeOH. The reaction mixture was dried under reduced pressure and the residue was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 4.5 mg (33 %) of the desired product. ¹H NMR (300 MHz, CD₃OD) δ 1.37 (d, 3H), 1.87 (s, 3H), 2.13 (s, 3H), 2.26 (m, 1H), 2.64 (m, 1H), 3.39 (m, 2H), 3.75 (s, 3H), 5.18 (s, 2H), 5.34 (m, 1H) ppm; ³¹P (121.4 MHz, CD₃OD) δ 21.47 ppm; MS (*m/z*) 422 [M-H]⁻, 424 [M+H]⁺.



Example 273: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated

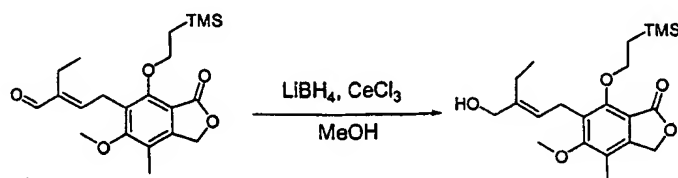
5 below.



2-Ethyl-4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-but-2-enal

A solution of [6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-acetaldehyde (1.5 g, 4.46 mmol) in toluene (14 mL) was heated at 100 °C with 2-(triphenyl-phosphanylidene)-butyraldehyde (1.68g, 5.35 mmol) overnight. A second portion of 2-(triphenyl-phosphanylidene)-butyraldehyde (495 mg, 1.49 mmol) was added and the reaction mixture was heated for an additional day. After concentration, the residue was purified by silica gel chromatography to provide 1.3g (83%) of the

desired product as oil. ^1H NMR (300 MHz, CDCl_3) δ 0.01 (s, 9H), 1.03 (t, 3H), 1.10- 1.21 (m, 2H), 2.15 (s, 3H), 2.15-2.44 (m, 2H), 3.67- 3.76 (m, 2H), 3.74 (s, 3H), 4.31- 4.36 (m, 2H), 5.10 (s, 2H), 6.34- 6.38 (m, 1H), 9.28 (s, 1H) ppm.

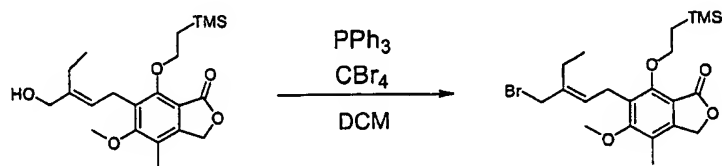


5

6-(3-Hydroxymethyl-pent-2-enyl)-5-methoxy-4-methyl-7-(2-trimethylsilylanil-ethoxy)-3H-isobenzofuran-1-one

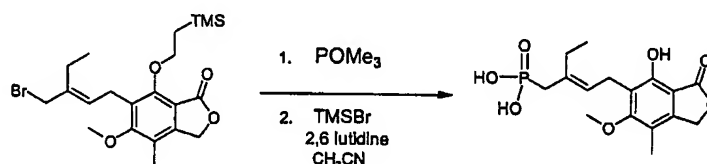
A solution of 2-ethyl-4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanil-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-but-2-enal (1.3g, 3.30 mmol) in methanol (10 mL) and THF (10 mL) was cooled to 0 °C. A solution of CeCl_3 (8.25 mL, 0.4M, $\text{MeOH}:\text{H}_2\text{O}$, 9:1) was added, followed by LiBH_4 (1.66 mL, 3.30 mmol of a 2M solution in THF). The ice bath was removed and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for an additional 40 minutes, whereupon TLC indicated complete consumption of starting aldehyde. The reaction was worked up by addition of aqueous 1N HCl and the product was extracted with EtOAc. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography to provide 948 mg (73%) of the product as colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 0.00 (s, 9H), 1.07 (t, 3H), 1.20 (dd, 2H, $J = 7, 8$ Hz), 2.13 (s, 3H), 2.38- 2.50 (m, 2H), 3.77 (s, 3H), 3.99 (s, 2H), 4.27 (dd, 2H, $J = 7, 8$ Hz), 5.08 (s, 2H), 5.34 (t, $J = 7.2$ Hz, 1H) ppm.

25



6-(3-Bromomethyl-pent-2-enyl)-5-methoxy-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one

Polymer-supported triphenylphosphine (3 mmol/g, 0.66 g) was soaked in dichloromethane (6 mL) for 1 hour. 6-(3-Hydroxymethyl-pent-2-enyl)-5-methoxy-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one (260 mg, 0.66 mmol) and carbon tetrabromide (657 mg, 1.98 mmol) were added sequentially and the mixture was shaken for 1 hour at room temperature. The mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel chromatography to provide 233 mg (77%) of the product as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 9H), 1.08 (t, 3H), 1.20 (dd, 2H, J = 7, 8 Hz), 2.14 (s, 3H), 2.35-2.43 (m, 2H), 3.44 (d, J = 7.2, 2H), 3.73 (s, 3H), 3.95 (s, 2H), 4.27 (dd, 2H, J = 7, 8 Hz), 5.08 (s, 2H), 5.53 (t, J = 7.2 Hz, 1H) ppm.



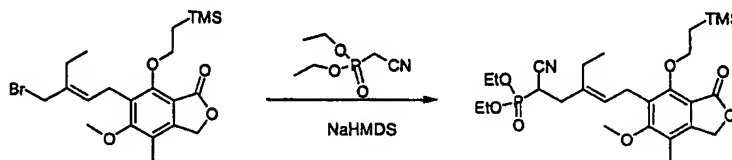
[2-Ethyl-4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-but-2-enyl]-phosphonic acid

A solution of 6-(3-bromomethyl-pent-2-enyl)-5-methoxy-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one (230 mg, 0.5 mmol) in trimethylphosphite (1.5 mL, 12.75 mmol) was heated to 100 °C for 4 hours. The reaction was worked up by removal of excess trimethylphosphite under reduced pressure. The residue was dissolved in acetonitrile (1 mL) and TMSBr (646 μL, 5.0 mmol) and 2,6-lutidine (580 μL, 5.0 mmol) were added at 0 °C. The reaction solution was allowed to warm to room temperature and stirred for 4 hours. The reaction was cooled to 0 °C and quenched with addition of MeOH. The reaction mixture was dried under reduced pressure and the residue was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 77mg (58%) of the product. ¹H NMR (300 MHz, CD₃OD) δ 1.08 (t, 3H), 2.16 (s, 3H), 2.43 (m, 2H), 2.48 (d, 2H, J = 22 Hz), 3.46 (t, 2H, J = 6

Hz), 3.79 (s, 3H), 5.25 (s, 2H), 5.38 (q, 1H, $J = 7$ Hz) ppm.; ^{31}P (121.4 MHz, CD_3OD) δ 25.65 ppm.; MS (m/z) 355 $[\text{M}-\text{H}]^-$, 357 $[\text{M}+\text{H}]^+$.

Example 274: Preparation of Representative Compounds of the Invention.

5 Representative compounds of the invention can be prepared as illustrated below.

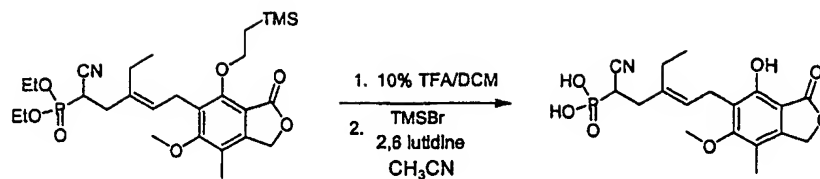


10 **{1-Cyano-3-ethyl-5-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-pent-3-enyl}-phosphonic acid diethyl ester**

To a solution of diethyl cyanomethylphosphonate (233 mg, 1.32 mmol) in THF (1 mL) was added a THF solution of sodium bis(trimethylsilyl)amide (1.0 M, 1.21 mL, 1.21 mmol). After stirring for 30 minutes, the solution was added dropwise to a solution of 6-(3-bromomethyl-pent-2-enyl)-5-methoxy-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one (100 mg, 0.22 mmol) in THF (1 mL). The resulting mixture was allowed to stir at room temperature overnight before saturated aqueous ammonium chloride was added. The reaction mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated to dryness. The residue was purified by preparative reverse-phase HPLC, affording 51 mg (42%) of the desired product.

^1H NMR (300 MHz, CDCl_3) δ 0.04 (s, 9H), 1.07 (t, 3H), 1.24 (dd, 2H, $J = 7, 8$ Hz), 1.36 (t, 6H), 2.12 (m, 1H), 2.18 (s, 3H), 2.35-2.47 (m, 2H), 2.67 (m, 1H), 3.00-3.14 (m, 1H), 3.44 (d, $J = 7.2$, 2H), 3.79 (s, 3H), 4.12-4.37 (m, 6H), 5.13 (s, 2H), 5.38 (t, $J = 7.2$ Hz, 1H) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 18.26 ppm; MS (m/z) 574 $[\text{M}+\text{Na}]^+$.

25



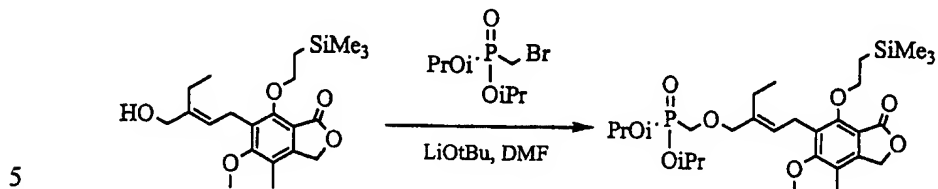
[1-Cyano-3-ethyl-5-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-pent-3-enyl]-phosphonic acid

5 {1-Cyano-3-ethyl-5-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-pent-3-enyl}-phosphonic acid diethyl ester (19.5 mg, 0.035 mmol) was dissolved in a solution of 10% TFA/ CH₂Cl₂ (2 mL) and stirred at room temperature for 10 minutes. The reaction mixture was dried under reduced pressure and purified by RP-HPLC to provide 9.5 mg (61%) of the desired product. This material was dissolved in DMF (0.5 mL) and DCM (0.5 mL) and TMSBr (27 μL, 0.2 mmol) and 2,6-lutidine (23 μL, 0.2 mmol) were added. The reaction solution was allowed stir at room temperature overnight before quenching with MeOH. The reaction mixture was dried under reduced pressure and the residue was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 5.1 mg (65%) of the desired product as a white solid. ¹H NMR (300 MHz, CD₃OD) δ 1.10 (t, 3H), 2.16 (s, 3H), 2.23-2.52 (m, 3H), 2.67 (m, 1H), 3.05-3.20 (m, 1H), 3.48 (d, *J* = 7.2, 2H), 3.81 (s, 3H), 5.26 (s, 2H), 5.43 (t, *J* = 7.2 Hz, 1H) ppm; ³¹P (121.4 MHz, CD₃OD) δ 14.18 ppm; MS (*m/z*) 394 [M-H]⁻, 396 [M+H]⁺.

20

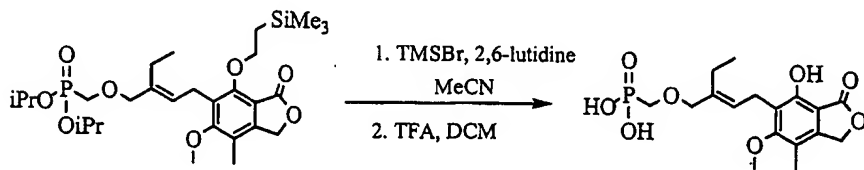
Example 275: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.



{2-Ethyl-4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-but-2-enyloxymethyl}-phosphonic acid diisopropyl ester

- 10 To a solution of bromomethylphosphonate diisopropyl ester (680mg, 2.62 mmol) and 6-(3-hydroxymethyl-pent-2-enyl)-5-methoxy-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one (688mg, 1.75 mmol) in DMF (3 mL) was added lithium t-butoxide (1.0M in THF; 2.6mL). The reaction was heated at 70°C for 2 hours. After cooling to ambient temperature, more
- 15 bromomethylphosphonate diisopropyl ester (680mg, 2.62 mmol) and lithium t-butoxide (1.0M in THF; 2.6mL) were added. The reaction mixture was heated at 70°C for a further hour, cooled, poured into a solution of lithium chloride (5% aqueous) and extracted with ethyl acetate. The organic extract was dried and the product was purified by chromatography on silica gel, eluting with hexane-ethyl
- 20 acetate to provide 347 mg (35%) of the product as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 0.04 (s, 9H), 1.09 (t, 3H, *J* = 7.5 Hz), 1.20- 1.26 (m, 2H), 1.31 (t, 12H, *J* = 6 Hz), 2.18 (s, 3H), 2.29 (q, 2H, *J* = 7.5 Hz), 3.5 (m, 2H), 3.59 (d, 2H, *J* = 8.7 Hz), 3.78 (s, 3H), 3.98 (s, 2H), 4.28- 4.35 (m, 2H), 4.6-4.8 (m, 2H), 5.13 (s, 2H), 5.4 (t, 1H, *J* = 7 Hz) ppm; ³¹P (121.4 MHz, CDCl₃) δ 20.26 ppm; MS
- 25 (*m/z*) 593.3 [M+Na]⁺.

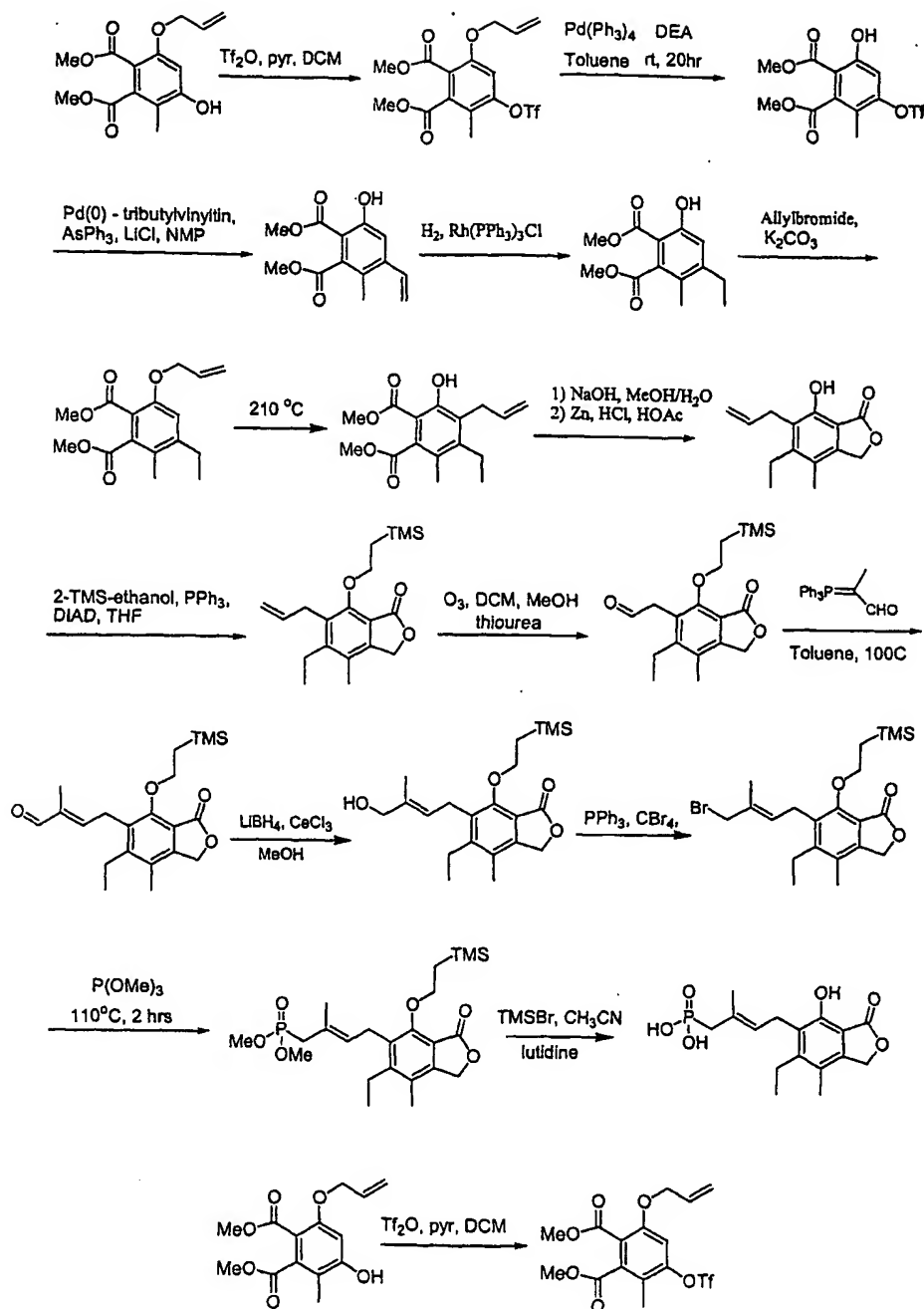


[2-Ethyl-4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-but-2-enyloxymethyl]-phosphonic acid

To a solution of {2-ethyl-4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-but-2-enyloxymethyl}-phosphonic acid diisopropyl ester (347mg, 0.61mmol) in acetonitrile (5mL) was added 2,6-lutidine (0.71mL, 6.1mmol) and bromotrimethylsilane (0.786mL, 6.1mmol). The mixture was stirred at room temperature for 3 hours, quenched with methanol (5mL), concentrated, and partitioned between ethyl acetate and 1N HCl (aqueous). The organic layer was concentrated to give the free phosphonic acid as a colorless oil (205mg, 70%). This material (20mg) was dissolved in a solution of trifluoroacetic acid (0.3mL) and dichloromethane (2.7mL) and stirred for 30 minutes at ambient temperature. After concentration, the residue was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide the product, after lyophilization, as a white solid (10mg). ¹H NMR (300 MHz, CDCl₃) δ 1.007 (t, 3H, J= 7.5 Hz), 2.13 (s, 3H), 2.32 (q, 2H, J= 7.5 Hz), 3.41 (d, 2H, J= 6.3 Hz), 3.56 (d, 2H, J= 9 Hz), 3.75 (s, 3H), 3.95 (s, 2H), 5.16 (s, 2H), 5.43 (t, 1H, J= 6.3 Hz) ppm; ³¹P (121.4 MHz, CDCl₃) δ 22.8 ppm; MS (m/z) 385.2 [M-H]⁺, 387.1 [M+H]⁺.

Example 276: Preparation of Representative Compounds of the Invention.

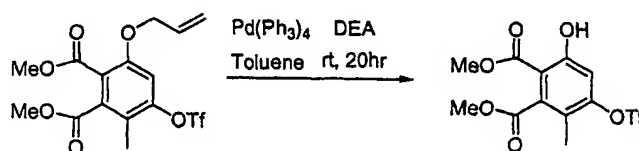
Representative compounds of the invention can be prepared as illustrated below.



5 6-Allyloxy-3-methyl-4-trifluoromethanesulfonyloxy-phthalic acid dimethyl ester

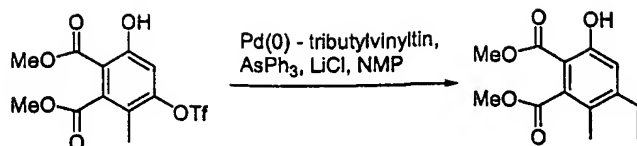
To a solution of 6-allyloxy-4-hydroxy-3-methyl-phthalic acid dimethyl ester (8.06 g, 28.8 mmol) [synthesized according to: J. W. Patterson,

Tetrahedron, **1993**, *49*, 4789-4798] and pyridine (11.4 g, 144.0 mmol) in dichloromethane (DCM) (20 mL) at 0°C was added triflic anhydride (12.19 g, 43.2 mmol). The reaction was stirred at 0°C for 2 hours after which additional triflic anhydride (3 mL) was added. Stirring at 0°C was continued for an additional hour. The reaction mixture was poured into a mixture of DCM and HCl (1N). The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over sodium sulfate. Filtration and evaporation of solvents *in vacuo* yielded a crude product, which was purified by silica gel chromatography to provide 8.39 g of the product as an oil. ¹H NMR (300 MHz, CDCl₃): δ = 2.32 (s, 3H), 3.89 (s, 6H), 4.60 (m, 2H), 5.33 (d, *J* = 9.3 Hz, 1H), 5.41 (d, *J* = 18.6 Hz, 1H), 5.95 (m, 1H), 6.95 (s, 1H) ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ = -74 ppm.



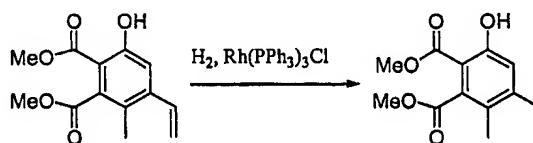
6-Hydroxy-3-methyl-4-trifluoromethanesulfonyloxy-phthalic acid dimethyl ester

To a solution of 6-allyloxy-3-methyl-4-trifluoromethanesulfonyloxy-phthalic acid dimethyl ester (8.39 g, 20.3 mmol) in toluene (20 mL) was added tetrakis(triphenylphosphine) palladium (0.47 g, 0.40 mmol) and diethylamine (2.97 g, 40.86 mmol) at room temperature under an atmosphere of nitrogen. Stirring at room temperature was continued until all starting material was consumed. The crude reaction mixture was partitioned between diethyl ether and HCl (0.1 N). The organic layer was washed with brine and dried over sodium sulfate. Filtration and evaporation of solvents *in vacuo* yielded a crude material, which was purified by silica gel chromatography to provide 4.16 g (55%) of the desired product as an off-white solid. ¹H NMR (300 MHz, CDCl₃): δ = 2.20 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 7.01 (s, 1H) ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ = -74 ppm.



6-Hydroxy-3-methyl-4-vinyl-phthalic acid dimethyl ester

To a solution of 6-hydroxy-3-methyl-4-trifluoromethanesulfonyloxy-phthalic acid dimethyl ester (2.17 g, 5.85 mmol) in *N*-methyl pyrrolidinone (15 mL) was added lithium chloride (743 mg, 17.5 mmol) and triphenylarsine (179 mg, 0.585 mmol). Tributylvinyltin (2.04 g, 6.43 mmol) was added followed by tris(triphenylideneacetone)dipalladium(0)-chloroform adduct (90 mg, 0.087 mmol). The reaction was placed under an atmosphere of nitrogen and heated at 60°C for 18 hours. The reaction was cooled to room temperature and poured onto a mixture of ice (20 g), EtOAc (40 mL), and potassium fluoride (1 g). Stirring was continued for 1 hour. The aqueous layer was extracted with EtOAc and the organic extracts filtered through Celite. The combined organic layers were washed with water and dried over sodium sulfate. Filtration and evaporation of solvents *in vacuo* yielded a crude material, which was purified by silica gel chromatography to provide 1.27 g (87%) of the product as an off-white solid. ¹H NMR (300 MHz, CDCl₃): δ = 2.16 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 5.46 (dd, *J* = 11.1, 1.2 Hz, 1H), 5.72 (dd, *J* = 17.1, 0.9 Hz, 1H), 6.86 (dd, *J* = 17.1, 11.1 Hz, 1H), 7.14 (s, 1H), 10.79 (s, 1H) ppm.

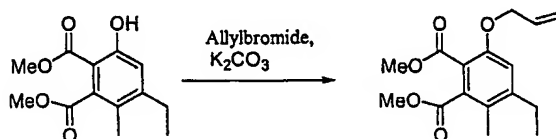


4-Ethyl-6-hydroxy-3-methyl-phthalic acid dimethyl ester

6-Hydroxy-3-methyl-4-vinyl-phthalic acid dimethyl ester (1.27 g, 5.11 mmol) was dissolved in benzene (10 mL) and EtOAc (10 mL). Tris(triphenylphosphine)rhodium chloride (150 mg) was added and the reaction was placed under an atmosphere of hydrogen. Stirring at room temperature was continued. After 14 hours, the solvents were removed *in vacuo* and the crude

material was purified by silica gel chromatography to provide 1.14 g (88%) of the desired product as an off-white solid. ^1H NMR (300 MHz, CDCl_3): δ = 1.19 (t, J = 7.8 Hz, 3H), 2.10 (s, 3H), 2.60 (q, J = 7.8 Hz, 2H), 3.89 (s, 6H), 6.87 (s, 1H), 10.79 (s, 1H) ppm.

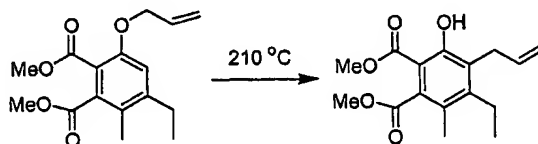
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1 6-Allyloxy-4-ethyl-3-methyl-phthalic acid dimethyl ester

4-Ethyl-6-hydroxy-3-methyl-phthalic acid dimethyl ester (1.01 g, 4.02 mmol) was dissolved in DMF (5 mL). Potassium carbonate (3.33 g, 24.14 mmol) was added, followed by allylbromide (2.92 g, 24.14 mmol). The suspension was heated at 60°C . After 14 hours, the reaction was cooled to room temperature and filtered. The solvents were removed *in vacuo* and the crude material was purified by silica gel chromatography to provide 0.976 g (83%) of the desired product as a colorless oil. ^1H NMR (300 MHz, CDCl_3): δ = 1.16 (t, J = 7.2 Hz, 3H), 2.20 (s, 3H), 2.62 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.57 (m, 2H), 5.26 (dd, J = 9.3, 1.5 Hz, 1H), 5.41 (dd, J = 13.5, 1.5 Hz, 1H), 5.98 (m, 1H), 6.82 (s, 1H) ppm.

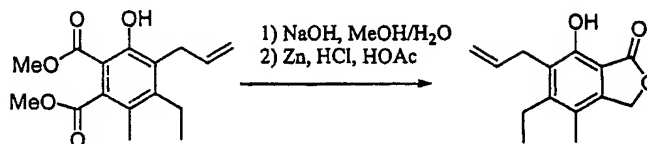
20



4-Allyl-5-ethyl-3-hydroxy-6-methyl-phthalic acid dimethyl ester

6-Allyloxy-4-ethyl-3-methyl-phthalic acid dimethyl ester (1.25 g, 4.28 mmol) was heated at 210°C under an atmosphere of nitrogen. After 14 hours, the reaction was cooled to room temperature. The crude material was purified by silica gel chromatography to provide 0.971 g (77%) of the desired product as a colorless oil. ^1H NMR (300 MHz, CDCl_3): δ = 1.14 (t, J = 7.8 Hz, 3H), 2.17 (s,

3H), 2.68 (q, $J = 7.8$ Hz, 2H), 3.49 (m, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 4.89 – 5.01 (m, 2H), 5.93 (m, 1H), 11.22 (s, 1H) ppm.

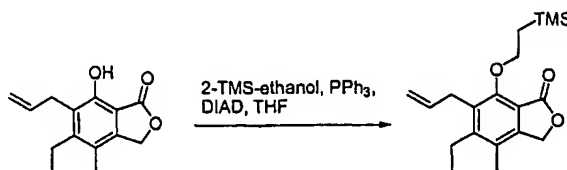


5

5 6-Allyl-5-ethyl-7-hydroxy-4-methyl-3H-isobenzofuran-1-one

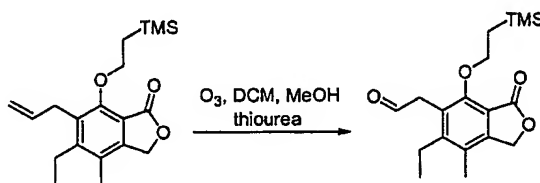
4-Allyl-5-ethyl-3-hydroxy-6-methyl-phthalic acid dimethyl ester (0.971 g, 3.32 mmol) was dissolved in MeOH (8 mL) at room temperature. A solution of sodium hydroxide (0.798 g, 19.95 mmol) in water (10 mL) was added and the suspension was heated at 55°C. After 16 hours, the reaction was cooled to room temperature and washed with diethyl ether. The aqueous layer was acidified (1N HCl) and the suspension was extracted with EtOAc. The combined organic layers were dried over sodium sulfate. Filtration and evaporation of solvents *in vacuo* yielded the desired bis acid as a white solid (0.846 g, 98%, $M^+ = 263$).

The bis acid was dissolved in acetic acid (6 mL) and HCl (conc., 1.5 mL). The reaction was heated at 80°C. Zn dust (0.635 g, 9.72 mmol, each) was added in portions every hour for 7 hours. Stirring at 80°C was continued for additional 10 hours. The reaction was cooled to room temperature, and water was added. The resultant suspension was extracted with EtOAc. The combined organic extracts were washed with sodium bicarbonate solution and dried over sodium sulfate. Filtration and evaporation of solvents *in vacuo* yielded the crude product, which was purified by silica gel chromatography to provide 0.375 g (50%) of the product as a white solid. ^1H NMR (300 MHz, CDCl_3): $\delta = 1.14$ (t, $J = 7.5$ Hz, 3H), 2.18 (s, 3H), 2.71 (q, $J = 7.5$ Hz, 2H), 3.49 (m, 2H), 4.95 (d, $J = 17.1$ Hz, 1H), 5.02 (d, $J = 10.2$ Hz, 1H), 5.23 (s, 2H), 5.98 (m, 1H), 7.66 (s, 1H) ppm.



5 6-Allyl-5-ethyl-4-methyl-7-(2-trimethylsilylanyl-ethoxy)-3H-isobenzofuran-1-one

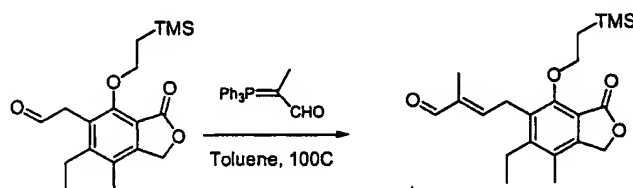
To a solution of 6-allyl-5-ethyl-7-hydroxy-4-methyl-3H-isobenzofuran-1-one (199 mg, 0.857 mmol), PPh₃ (337 mg, 1.286 mmol), and 2-trimethylsilylethanol in THF (3 mL) at 0°C was added diisopropyl azodicarboxylate (259 mg, 1.286 mmol). The resulting yellow solution was allowed to warm to room temperature and stirred for one hour. The solvent was removed *in vacuo* and the crude material was dissolved in diethyl ether (3 mL). Hexanes (1.5 mL) were added. Triphenylphosphine oxide was removed by filtration and the filtrate was concentrated and purified by silica gel chromatography to provide the desired product (261 mg, 92 %) as a clear oil. ¹H NMR (300 MHz, CDCl₃): δ = 0.04 (s, 9H), 1.15 (t, *J* = 7.8 Hz, 3H), 1.25 (m, 2H), 2.20 (s, 3H), 2.73 (q, *J* = 7.8 Hz, 2H), 3.54 (m, 2H), 4.28 (m, 2H), 4.95 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 5.15 (s, 2H), 5.95 (m, 1H) ppm.



[6-Ethyl-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydroisobenzofuran-5-yl]-acetaldehyde

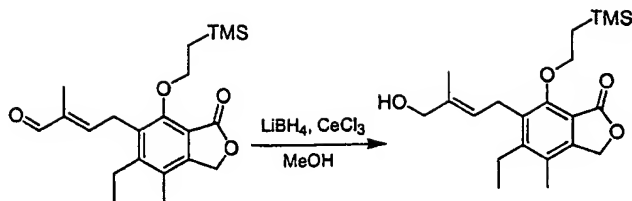
A solution of 6-allyl-5-ethyl-4-methyl-7-(2-trimethylsilylanyl-ethoxy)-3H-isobenzofuran-1-one (261 mg, 0.788 mmol) in MeOH (5 mL), CH₂Cl₂ (5 mL) and pyridine (50 μL) was cooled to -78°C using a dry ice/acetone bath according to the procedure of Smith, D. B. *et al.*, *J. Org. Chem.*, **1996**, *61*, 6, 2236. A stream of ozone was bubbled through the reaction *via* a gas dispersion tube until the reaction became blue in color (15 minutes). The ozone line was replaced with a stream of nitrogen and bubbling continued for another 15 minutes, by which time the blue color had disappeared. To this solution, at -78°C, was added thiourea (59.9 mg, 0.788 mmol) in one portion, and the cooling bath was removed. The reaction was allowed to warm to room temperature and

stirred for 15 hours. The reaction mixture was filtered and then partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 one more time and the organic extracts were combined, washed with aqueous 1N HCl, saturated NaHCO_3 and brine and dried over sodium sulfate. Filtration and evaporation of solvents in vacuo yielded the crude product, which was purified by silica gel chromatography to afford 181 mg (69 %) of the product as a white solid. ^1H NMR (300 MHz, CDCl_3): δ = 0.04 (s, 9H), 1.11 (t, J = 7.5 Hz, 3H), 1.19 (m, 2H), 2.21 (s, 3H), 2.66 (q, J = 7.5 Hz, 2H), 3.90 (s, 2H), 4.36 (m, 2H), 5.18 (s, 2H), 9.71 (s, 1H) ppm.



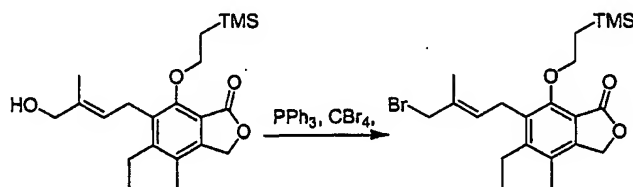
4-[6-Ethyl-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enal

[6-Ethyl-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-acetaldehyde (90 mg, 0.269 mmol) and 2-(triphenyl-phosphorylidene)-propionaldehyde (72.9 mg, 0.23 mmol) in toluene (3 mL) were heated at 100°C. After 15 hours, a second portion of 2-(triphenyl-phosphanylidene)-propionaldehyde (33 mg, 0.11 mmol) was added and the reaction mixture was heated for additional 9 hours. The toluene was removed *in vacuo*, and the residue was purified by silica gel chromatography to provide 77.6 mg (77%) of the desired product as a pale yellow oil. ^1H NMR (300 MHz, CDCl_3): δ = 0.03 (s, 9H), 1.15 (t, J = 7.5 Hz, 3H), 1.21 (m, 2H), 1.93 (s, 3H), 2.21 (s, 3H), 2.71 (q, J = 7.5 Hz, 2H), 3.82 (d, J = 6.9 Hz, 2H), 4.34 (m, 2H), 5.18 (s, 2H), 6.38 (m, 1H), 9.35 (s, 1H) ppm.



5-Ethyl-6-(4-hydroxy-3-methyl-but-2-enyl)-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one

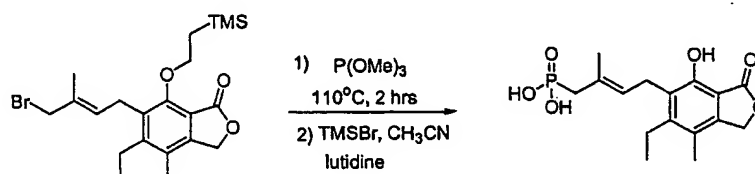
4-[6-Ethyl-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enal (77.6 mg, 0.207 mmol) was dissolved in MeOH (4 mL). A solution of CeCl_3 (51.1 mg, 0.207 mmol) in MeOH/water (9/1, 0.66 mL) was added and the solution was cooled to 0°C . A solution of lithium borohydride in THF (2M, 0.105 mL) was added dropwise. After 15 minutes, the reaction was quenched with 1N HCl (0.5 mL). The MeOH was removed *in vacuo* and the crude material was partitioned between DCM and water. The aqueous layer was extracted with DCM and the combined organic layers were washed with sodium bicarbonate solution and dried over sodium sulfate. Filtration and evaporation of solvents yielded a crude oil, which was purified by silica gel chromatography to provide 57.2 mg (73%) of the desired product. ^1H NMR (300 MHz, CDCl_3): δ = 0.04 (s, 9H), 1.15 (t, J = 7.8 Hz, 3H), 1.26 (m, 2H), 1.86 (s, 3H), 2.19 (s, 3H), 2.72 (q, J = 7.8 Hz, 2H), 3.52 (d, J = 6.3 Hz, 2H), 3.99 (s, 2H), 4.34 (m, 2H), 5.14 (s, 2H), 5.32 (m, 1H) ppm.



6-(4-Bromo-3-methyl-but-2-enyl)-5-ethyl-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one

5-Ethyl-6-(4-hydroxy-3-methyl-but-2-enyl)-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one (57.2 mg, 0.152 mmol) was dissolved in DCM (3.5 mL). Polymer-bound triphenylphosphine (3 mmol/g, 152.1 mg) was added and the mixture was mechanically stirred at room

temperature. Carbon tetrabromide (151.3 mg, 0.456 mmol) was added and the solution was stirred at room temperature. After 2 hours, the reaction was filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography to provide 58.0 mg (87%) of the desired product. ¹H NMR (300 MHz, CDCl₃): δ = 0.04 (s, 9H), 1.15 (t, *J* = 7.8 Hz, 3H), 1.25 (m, 2H), 1.95 (s, 3H), 2.20 (s, 3H), 2.70 (q, *J* = 7.8 Hz, 2H), 3.52 (d, *J* = 6.3 Hz, 2H), 3.94 (s, 2H), 4.28 (m, 2H), 5.14 (s, 2H), 5.50 (m, 1H) ppm.



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{4-[6-Ethyl-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-phosphonic acid

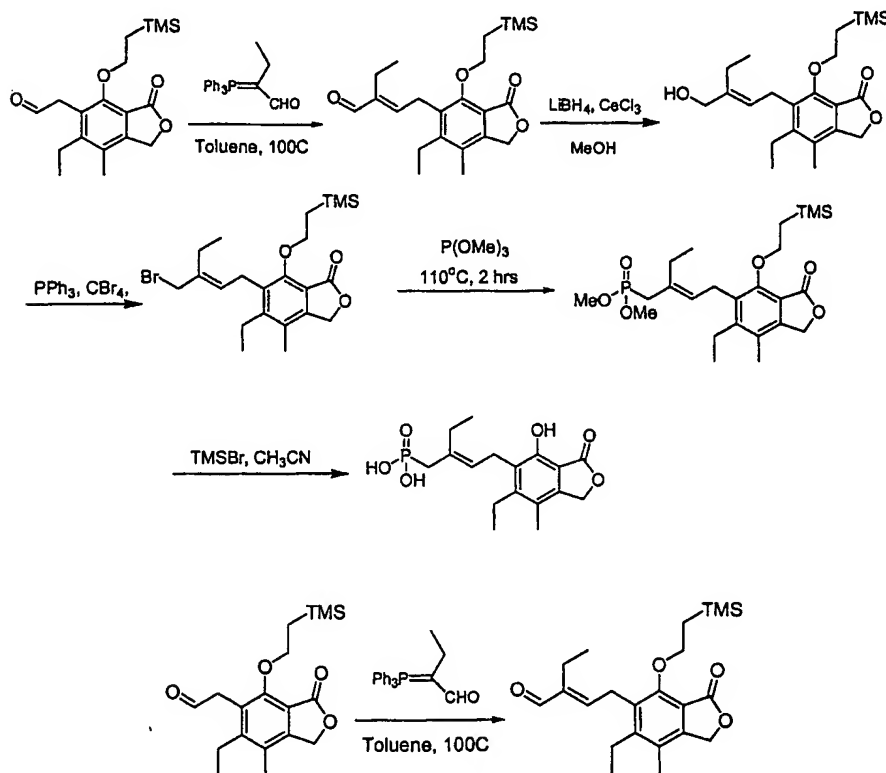
A solution of 4-[6'-ethyl-7'-methyl-3'-oxo-4'-(2''-trimethylsilyl-ethoxy)-1',3'-dihydro-isobenzofuran-5'-yl]-2-methyl-but-2-enyl bromide (58 mg, 0.132 mmol) in trimethylphosphite (0.8 mL) was heated at 110°C. After 2 hours the reaction was complete. The reaction was cooled to room temperature and the excess trimethylphosphite was removed *in vacuo*. The crude material was used in the next step without further purification.

The crude product of the Arbuzov reaction was dissolved in MeCN (0.8 mL). Trimethylsilyl bromide (202.2 mg, 1.321 mmol) was added and the reaction was stirred at room temperature. After 15 minutes, lutidine (155.7 mg, 1.453 mmol) was added and stirring at room temperature was continued. After 2 hours, additional trimethylsilyl bromide (202.2 mg, 1.321 mmol) was added and stirring at room temperature was continued. After 4 hours, the reaction was quenched with MeOH (2 mL). The solvents were evaporated *in vacuo*, and the crude material was purified by RP-HPLC (eluent: water / MeCN). The product-containing fractions were combined and lyophilized to yield 2.3 mg (5.1%) of the free phosphonic acid. ¹H NMR (300 MHz, DMSO-d₆): δ = 1.07 (t, *J* = 7.5 Hz, 3H), 1.84 (s, 3H), 2.14 (s, 3H), 2.64 (q, *J* = 7.5 Hz, 2H), 3.34 (m, 4H), 5.06

(m, 1H), 5.25 (s, 2H) ppm; ^{31}P NMR (121 MHz, DMSO- d_6): δ = 22.19 ppm;
MS = 341 [M^+ +1].

Example 277: Preparation of Representative Compounds of the Invention.

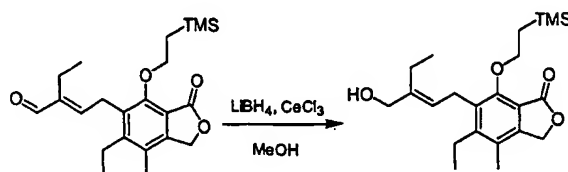
5 Representative compounds of the invention can be prepared as illustrated below.



[2-Ethyl-4-[6-ethyl-7-methyl-3-oxo-4-(2-trimethylsilanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-but-2-enal

15 [6-Ethyl-7-methyl-3-oxo-4-(2-trimethylsilanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-acetaldehyde (90 mg, 0.269 mmol) and 2-(triphenyl-phosphorylidene)-butyraldehyde (98.4 mg, 0.296 mmol) in toluene (3 mL) were heated at 100°C . After 15 hours, a second portion of 2-(triphenyl-phosphanylidene)-butyraldehyde (98.4 mg, 0.296 mmol) was added and the reaction mixture was heated for additional 33 hours. After concentration, the

residue was purified by silica gel chromatography to provide 50.3 mg (48%) of the desired product as a pale yellow oil.

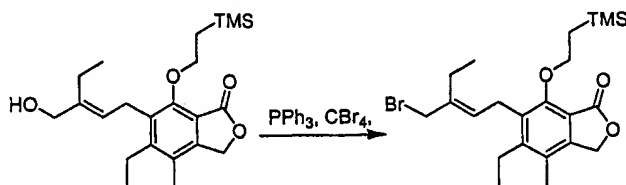


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5-Ethyl-6-(3-hydroxymethyl-pent-2-enyl)-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one

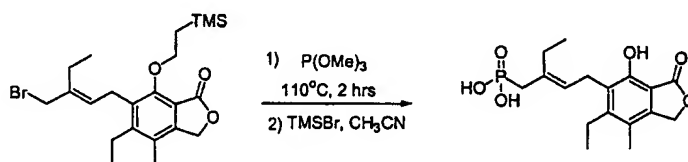
2-Ethyl-4-[6-ethyl-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-but-2-enal (50.3 mg, 0.129 mmol) was dissolved in MeOH (3 mL). A solution of CeCl_3 (31.9 mg, 0.129 mmol) in MeOH/water (9/1, 0.66 mL) was added and the solution was cooled to 0°C . A solution of lithium borohydride in THF (2M, 0.065 mL) was added dropwise. After 10 minutes, the reaction was quenched with 1N HCl (0.5 mL). The methanol was removed *in vacuo* and the crude material was partitioned between DCM and water. The aqueous layer was extracted with DCM and the combined organic layers were washed with sodium bicarbonate solution and were dried over sodium sulfate. Filtration and evaporation of solvents *in vacuo* yielded a crude oil, which was purified by silica gel chromatography to provide 35.4 mg (70%) of the desired product. ^1H NMR (300 MHz, CDCl_3): δ = 0.04 (s, 9H), 1.10 – 1.19 (m, 6H), 1.26 (m, 2H), 2.19 (s, 3H), 2.32 (q, J = 7.5 Hz, 2H), 2.72 (q, J = 7.5 Hz, 2H), 3.54 (d, J = 6.6 Hz, 2H), 4.05 (s, 2H), 4.26 (m, 2H), 5.14 (s, 2H), 5.27 (m, 1H) ppm.

25



6-(3-Bromomethyl-pent-2-enyl)-5-ethyl-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one

5-Ethyl-6-(3-hydroxymethyl-pent-2-enyl)-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one (35.4 mg, 0.090 mmol) was dissolved in DCM (3.0 mL). Polymer-bound triphenylphosphine (3 mmol/g, 90.7 mg) was added, and the mixture was mechanically stirred at room temperature. Carbon tetrabromide (90.2 mg, 0.272 mmol) was added and the solution was stirred at room temperature. After 2 hours, the reaction was filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography to provide 32.0 mg (78%) of the desired product. The material was used in the next step without further characterization.



[2-Ethyl-4-(6-ethyl-4-hydroxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-but-2-enyl]-phosphonic acid

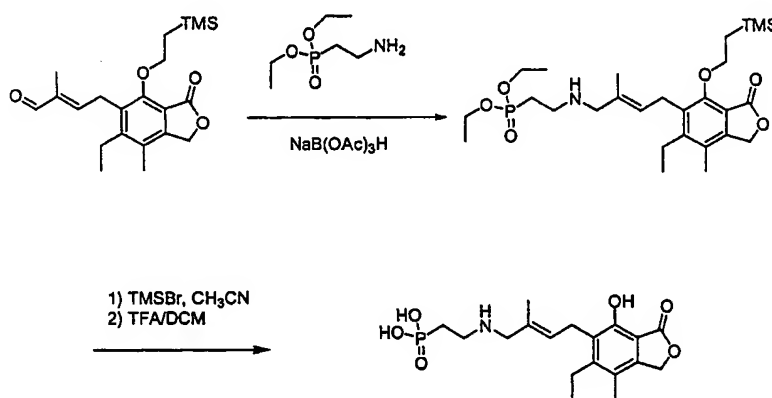
A solution of 6-(3-bromomethyl-pent-2-enyl)-5-ethyl-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one (32 mg, 0.070 mmol) in trimethylphosphite (0.8 mL) was heated at 110 °C. After 2 hours, the reaction was complete. The reaction was cooled to room temperature and the excess trimethylphosphite was removed *in vacuo*. The crude material was used in the next step without further purification.

The crude product of the Arbuzov reaction was dissolved in MeCN (0.8 mL). Trimethylsilyl bromide (108.0 mg, 0.706 mmol) was added and the reaction was stirred at room temperature. After 2 hours, a second batch of trimethylsilyl bromide (108.0 mg, 0.706 mmol) was added. After 3 hours, the reaction was quenched with MeOH (2 mL). The solvents were evaporated *in vacuo* and the crude material was purified by RP-HPLC (eluent: water / MeCN). The product-containing fractions were combined and lyophilized to yield 15.7 mg (63%) of the product. ¹H NMR (300 MHz, DMSO-d₆): δ = 0.98 - 1.09 (m,

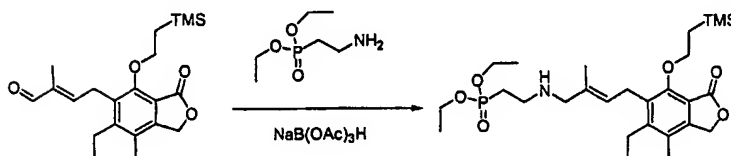
6H), 2.10 (s, 3H), 2.30 (m, 2H), 2.64 (q, $J = 7.5$ Hz, 2H), 3.38 (m, 4H), 5.03 (m, 1H), 5.25 (s, 2H) ppm; ^{31}P NMR (121 MHz, DMSO- d_6): $\delta = 22.26$ ppm; MS = 355 [$\text{M}^+ + 1$].

5 Example 278: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.



10



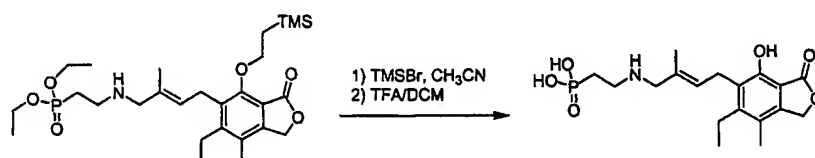
(2-{4-[6-Ethyl-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino}-ethyl)-phosphonic acid diethyl ester

15

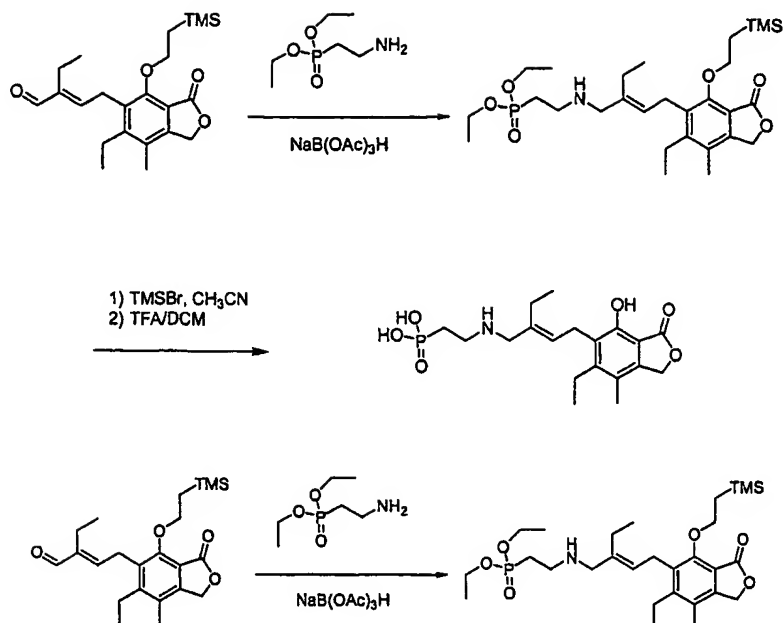
4-[6-Ethyl-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enal (19.7 mg, 0.052 mmol) and aminoethylphosphonic acid diethylester oxalate salt (15.6 mg, 0.057 mmol) were dissolved in DMF (0.5 mL). Acetic acid (15.7 mg, 0.263 mmol) was added, followed by sodium triacetoxyborohydride (22.3 mg, 0.105 mmol). After 4 hours, the crude reaction mixture was purified by RP-HPLC (eluent: water/MeCN) to provide 27.7 mg (97%) of the desired product after

20

lyophilization. ^1H NMR (300 MHz, CDCl_3): δ = 0.04 (s, 9H), 1.14 (t, J = 7.5 Hz, 3H), 1.26 (m, 2H), 1.30 (t, J = 7.2 Hz, 6H), 1.95 (s, 3H), 2.19 (s, 3H), 2.23 (m, 2H), 2.68 (q, J = 7.5 Hz, 2H), 3.18 (m, 2H), 3.53 (s, 2H), 4.13 (m, 4H), 4.28 (m, 2H), 5.15 (s, 2H), 5.51 (m, 1H) ppm; ^{31}P NMR (121 MHz, CDCl_3): δ = 27.39 ppm; MS = 540 [M^+ +1].



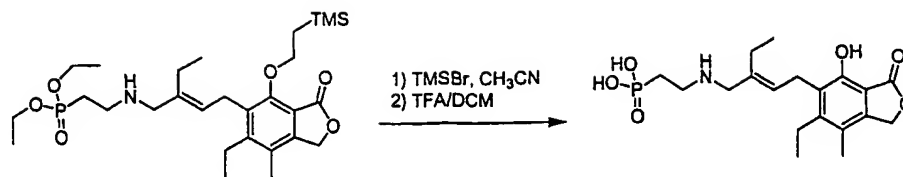
- {2-[4-(6-Ethyl-4-hydroxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enylamino]-ethyl}-phosphonic acid:**
- (2-{4-[6-Ethyl-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enylamino}-ethyl)-phosphonic acid diethyl ester (27.7 mg, 0.051 mmol) was dissolved in DMF (0.5 mL) and DCM (0.5 mL). Trimethylsilyl bromide (78.3 mg, 0.512 mmol) was added and the reaction was stirred at room temperature. After 20 hours, the reaction was quenched with MeOH (0.3 mL). The solvents were evaporated *in vacuo* and the crude material was purified by RP-HPLC (eluent: water/MeCN). The product-containing fractions were combined and lyophilized to yield 14.2 mg (57%) of the free phosphonic acid [MS: 484 M^+ +1].
- The material was dissolved in DCM (0.5 mL). TFA (0.05 mL) was added and stirring at room temperature was continued. After 20 minutes, the solvents were removed *in vacuo* and the crude material was purified by RP-HPLC (eluent: water/MeCN * 0.1% TFA). The product-containing fractions were combined and lyophilized to yield 7.6 mg (52%) of the product as the TFA salt. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.07 (t, J = 7.5 Hz, 3H), 1.84 (s, 3H), 1.90 (m, 2H), 2.11 (s, 3H), 2.63 (q, J = 7.5 Hz, 2H), 2.99 (m, 2H), 3.43 (d, J = 6.3 Hz, 2H), 3.51 (s, 2H), 5.26 (s, 2H), 5.45 (m, 1H) ppm; ^{31}P NMR (121 MHz, DMSO-d_6): δ = 20.02 ppm; MS = 384 [M^+ +1].



5 (2-{2-Ethyl-4-[6-ethyl-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-but-2-enylamino}-ethyl)-phosphonic acid diethyl ester

2-Ethyl-4-[6-ethyl-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-but-2-enal (26.6 mg, 0.068 mmol) and
 10 aminoethylphosphonic acid diethylester oxalate salt (20.4 mg, 0.075 mmol) were dissolved in DMF (0.8 mL). Acetic acid (20.5 mg, 0.342 mmol) was added, followed by sodium triacetoxyborohydride (27.6 mg, 0.137 mmol). After 8 hours, the crude reaction mixture was purified by RP-HPLC (eluent: water/MeCN) to provide 24.9 mg (65%) of the desired product after
 15 lyophilization. ¹H NMR (300 MHz, CDCl₃): δ = 0.05 (s, 9H), 1.10 - 1.24 (m, 8H), 1.35 (t, *J* = 7.5 Hz, 6H), 2.19 (s, 3H), 2.23 (m, 2H), 2.35 (q, *J* = 7.8 Hz, 2H), 2.70 (q, *J* = 7.2 Hz, 2H), 3.25 (m, 2H), 3.56 (m, 4H), 4.15 (m, 4H), 4.29 (m, 2H), 5.15 (s, 2H), 5.47 (m, 1H) ppm; ³¹P NMR (121 MHz, CDCl₃): δ = 27.71 ppm; MS = 554 [M⁺+1].

20



{2-[2-Ethyl-4-(6-ethyl-4-hydroxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-but-2-enylamino]-ethyl}-phosphonic acid

5 (2-{2-Ethyl-4-[6-ethyl-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-but-2-enylamino}-ethyl)-phosphonic acid diethyl ester (24.9 mg, 0.045 mmol) was dissolved in DMF (0.5 mL) and DCM (0.5mL). Trimethylsilyl bromide (68.7 mg, 0.449 mmol) was added and the reaction was stirred at room temperature. After 20 hours, the reaction was

10 quenched with MeOH (0.15 mL). The solvents were evaporated *in vacuo* and the crude material was purified by RP-HPLC (eluent: water/MeCN). The product-containing fractions were combined and lyophilized to yield 8.0 mg of the free phosphonic acid [MS: 498 $M^+ + 1$].

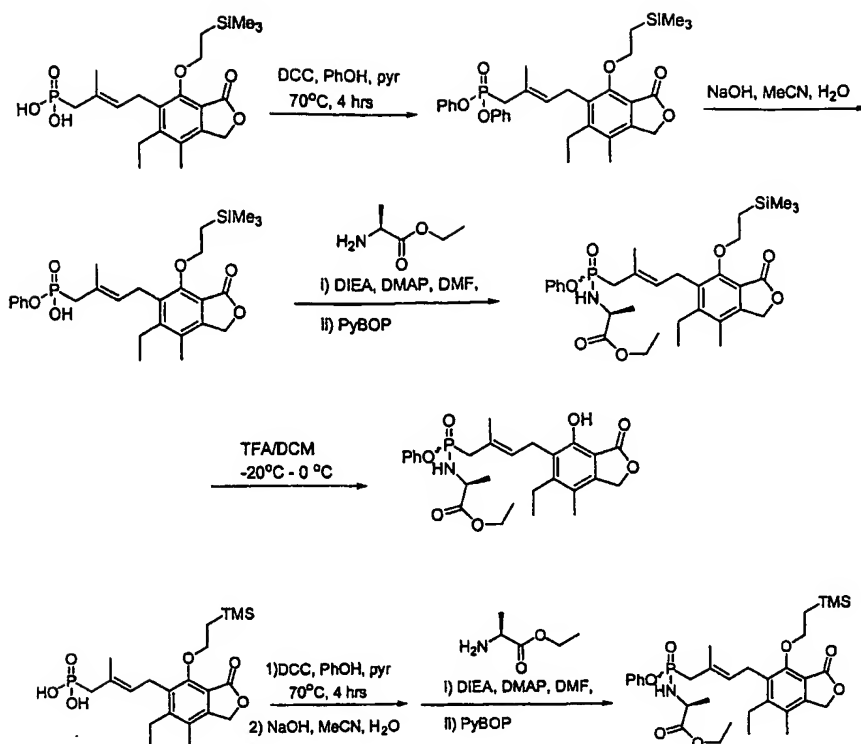
This material was dissolved in DCM (0.5 mL). TFA (0.05 mL) was

15 added, and stirring at room temperature was continued. After 20 minutes, the solvents were removed *in vacuo* and the crude material was purified by RP-HPLC (eluent: water/MeCN * 0.1% TFA). The product-containing fractions were combined and lyophilized to yield 4.4 mg (54%) of the product as the TFA salt. ^1H NMR (300 MHz, DMSO- d_6): δ = 1.05 (m, 6H), 1.60 (m, 2H), 2.10 (s,

20 3H), 2.67 (q, J = 7.5 Hz, 2H), 2.63 (q, J = 6.9 Hz, 2H), 2.93 (m, 2H), 3.45 (m, 4H), 5.24 (s, 2H), 5.36 (m, 1H) ppm.; ^{31}P NMR (121 MHz, DMSO- d_6): δ = 16.93 ppm; MS = 398 [$M^+ + 1$].

Example 279: Preparation of Representative Compounds of the Invention.

25 Representative compounds of the invention can be prepared as illustrated below.



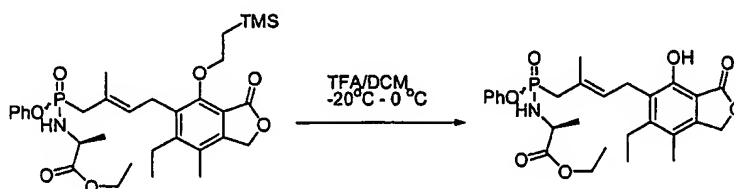
2-((4-[6-Ethyl-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydroisobenzofuran-5-yl]-2-methyl-but-2-enyl)-phenoxy-phosphinoylamino)-propionic acid ethyl ester

4-[6'-ethyl-7'-methyl-3'-oxo-4'-(2''-trimethylsilyl-ethoxy)-1',3'-dihydroisobenzofuran-5'-yl]-2-methyl-but-2-en-phosphonic acid (44.8 mg, 0.101 mmol), dicyclohexylcarbodiimide (52.6 mg, 0.254 mmol), and phenol (95.8 mg, 1.018 mmol) were dissolved in pyridine (0.3 mL) and heated at 70°C for 4 hours. The reaction mixture was cooled to room temperature and the pyridine was removed *in vacuo*. The crude material was partitioned between DCM and HCl (0.1N). The aqueous layer was extracted with DCM and the combined organic layers were dried over sodium sulfate. Filtration and evaporation of solvents *in vacuo* yielded a crude material, which was used in the next step without further purification.

The crude material was dissolved in MeCN (0.8 mL) and water (0.3 mL). Aqueous sodium hydroxide solution (2N, 0.8 mL) was added in portions (0.2 mL). After all starting material was consumed, the organic solvent was removed

in vacuo and the crude material was partitioned between chloroform and aqueous HCl (1N). The aqueous layer was extracted with chloroform. The combined organic layers were dried over sodium sulfate. Filtration and evaporation of solvents yielded the crude product as a mixture of mono phenyl ester and the symmetrical anhydride.

The crude material of the previous step and ethyl (*L*)-alanine hydrochloride salt (78.1 mg, 0.509 mmol) were dissolved in DMF (0.4 mL). DMAP (1.2 mg, catalytic) was added, followed by diisopropylethylamine (131.3 mg, 1.018 mmol). Stirring at room temperature was continued. After 20 minutes, complete conversion of the anhydride was observed. After 2 hours, PyBOP (101 mg, 0.202 mmol) was added and stirring at room temperature was continued. The reaction was filtered and the crude reaction solution was purified by RP-HPLC (eluent: water/MeCN). The product-containing fractions were combined and lyophilized to yield the product (15.7 mg, 25% over three steps) as a white powder. ^1H NMR (300 MHz, CDCl_3): δ = 0.03 (s, 9H), 1.13 – 1.28 (m, 8H), 2.03 (s, 3H), 2.19 (s, 3H), 2.62 – 2.74 (m, 4H), 3.38 (m, 1H), 3.53 (t, J = 6.3 Hz, 2H), 4.03 (m, 3H), 4.30 (m, 2H), 5.14 (s, 2H), 5.31 (m, 1H), 7.11 – 7.17 (m, 3H), 7.25 – 7.30 (m, 2H) ppm; ^{31}P NMR (121 MHz, CDCl_3): δ = 27.04, 27.73 ppm; MS = 615 [$\text{M}^+ + 1$].



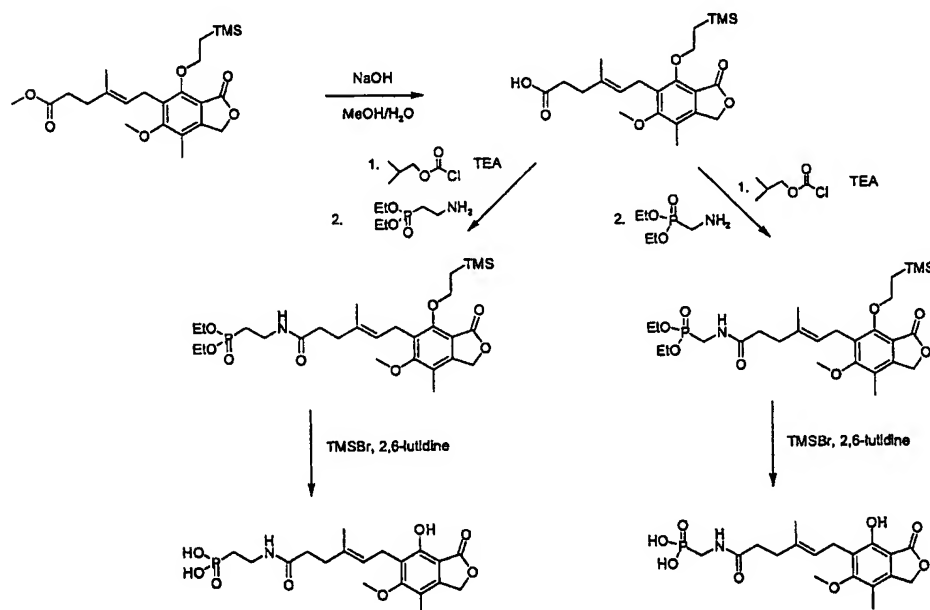
2-([4-(6-Ethyl-4-hydroxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyl]-phenoxy-phosphinoylamino)-propionic acid ethyl ester

2-([4-[6-Ethyl-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl]-phenoxy-phosphinoylamino)-propionic acid ethyl ester (7.5 mg, 0.012 mmol) was dissolved in TFA/DCM (10%, 0.3 mL) at -20°C . The reaction mixture was

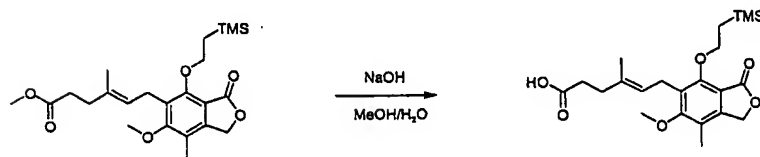
warmed to 0°C and stirred at this temperature for 45 minutes. Pyridine (0.09 mL) was added the solvents were removed *in vacuo*. The crude material was purified by RP-HPLC (eluent: water/MeCN). The product-containing fractions were combined and lyophilized, yielding a white powder (5.5 mg, 87%). ¹H NMR (300 MHz, CDCl₃): δ = 1.12 – 1.29 (m, 6H), 2.03 (s, 3H), 2.17 (s, 3H), 2.65 – 2.74 (m, 4H), 3.38 (m, 1H), 3.53 (t, *J* = 6.3 Hz, 2H), 4.03 (m, 3H), 5.22 (s, 2H), 5.36 (m, 1H), 7.11 – 7.16 (m, 3H), 7.24 – 7.30 (m, 2H), 7.72 (m, 1H) ppm; ³¹P NMR (121 MHz, CDCl₃): δ = 27.11, 27.57 ppm; MS = 515 [M⁺+1].

10 **Example 280: Preparation of Representative Compounds of the Invention.**

Representative compounds of the invention can be prepared as illustrated below.

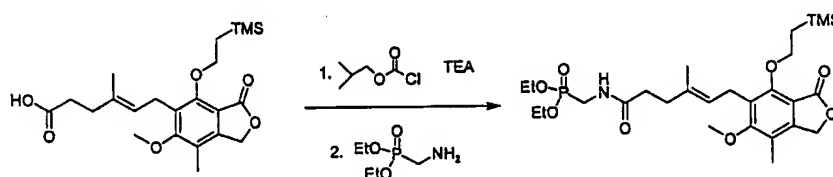


15



6-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid

A mixture of 6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid methyl ester (1.5 g, 3.45 mmol) and sodium hydroxide (552 mg) in a mixture of methanol (20 mL) and water (7 mL) was stirred at room temperature for one hour. The solution was acidified with 1N HCl. The precipitate was collected by suction filtration and washed with water to give the desired product (1.2g, 83%). ¹H NMR (300 MHz, CDCl₃) δ 0.02 (s, 9H), 1.15- 1.22 (m, 2H), 1.76 (s, 3H), 2.13 (s, 3H), 2.12- 2.28 (m, 2H), 2.35- 2.41 (m, 2H), 3.37 (d, 2H, J= 7 Hz), 3.71 (s, 3H), 4.22- 4.28 (m, 2H), 5.07 (s, 2H), 5.13- 5.17 (m, 1H) ppm; MS (m/z) 419.3 [M-H]⁻, 443.2 [M+Na]⁺.

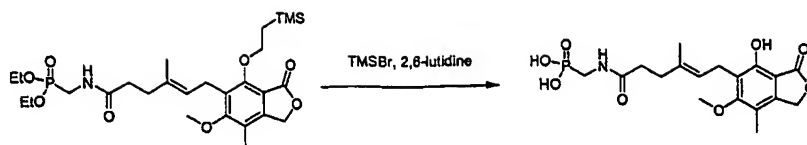


15

((6-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoylamino)-methyl)-phosphonic acid diethyl ester

To a solution of 6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid (50 mg, 0.12 mmol) in THF (1 mL) was added isobutyl chloroformate (17 μL, 0.13 mmol) and triethylamine (50 μL, 0.36 mmol) at 0°C. After stirring at 0°C for 2 hours, diethyl (aminomethyl) phosphonate oxalate (62 mg, 0.26 mmol) was added and stirring was continued at room temperature for 20 minutes. After removal of solvent, the residue was purified by preparative reverse-phase HPLC to afford 54.8 mg (81%) of the desired product. ¹H NMR (300 MHz, CDCl₃) δ 0.03 (s, 9H), 1.15- 1.22 (m, 2H), 1.31 (t, 6H), 1.81 (s, 3H), 2.18 (s, 3H), 2.30 (m, 4H), 3.41 (d, 2H, J= 7 Hz), 3.65 (dd, 2H, J= 6, 12 Hz), 3.77 (s, 3H), 3.77-4.16 (m, 4H), 4.26-4.32 (m, 2H), 5.12 (s, 2H), 5.17- 5.19 (m, 1H), 5.86 (bs, 1H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 23.01 ppm; MS (m/z) 568 [M-H]⁻, 592 [M+Na]⁺.

30

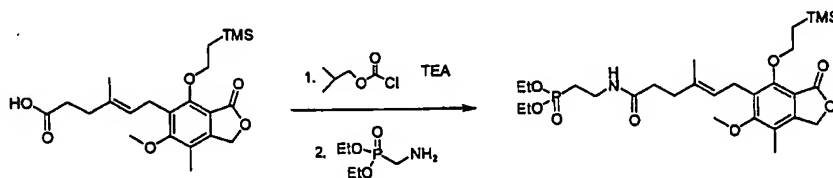


{{[6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoylamino]-methyl}-phosphonic acid

To a solution of ((6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoylamino)-methyl)-phosphonic acid diethyl ester (40 mg, 0.07 mmol) in acetonitrile (1 mL) was added TMSBr (91 μ L, 0.7 mmol) followed by 2,6-lutidine (81.5 μ L, 0.7 mmol). The reaction was allowed to proceed overnight when it was completed as judged by LCMS. The reaction mixture was quenched with MeOH and concentrated to dryness. The residue was purified by preparative reverse-phase HPLC to afford 2.6 mg (9%) of desired product as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 1.67 (s, 3H), 2.17 (m, 5H), 2.30-2.46 (m, 2H), 2.80- 2.86 (m, 2H), 3.55 (m, 2H), 3.82 (s, 3H), 5.26 (s, 3H) ppm; ^{31}P (121.4 MHz, CD_3OD) δ 10.27 ppm; MS (m/z) 412 $[\text{M}-\text{H}]^-$, 414 $[\text{M}+\text{H}]^+$.

Example 281: Preparation of Representative Compounds of the Invention.

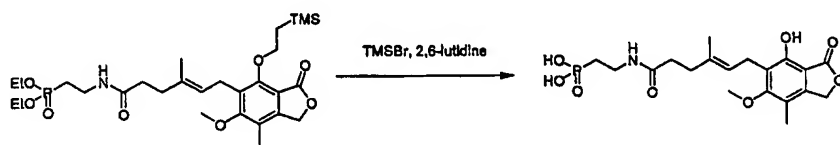
Representative compounds of the invention can be prepared as illustrated below.



(2-{6-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoylamino}-ethyl)-phosphonic acid diethyl ester

To a solution of 6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid (50 mg,

0.12 mmol) in THF (1 mL) was added isobutyl chloroformate (17 μ L, 0.13 mmol) and triethylamine (50 μ L, 0.36 mmol) at 0°C. After stirring at 0°C for 2 hours, diethyl (aminoethyl) phosphonate oxalate (62 mg, 0.26 mmol) was added and stirred at room temperature was continued for one hour. After removal of solvent, the residue was purified by preparative reverse-phase HPLC to afford 37 mg (54%) of the desired product as a white solid. ^1H NMR (300 MHz, CDCl_3) δ 0.03 (s, 9H), 1.15-1.22 (m, 2H), 1.31 (t, 6H), 1.81 (s, 3H), 1.85-1.93 (m, 2H), 2.18 (s, 3H), 2.30 (m, 4H), 3.41 (d, 2H, $J = 7$ Hz), 3.48-3.54 (m, 2H), 3.77 (s, 3H), 3.77-4.16 (m, 4H), 4.26-4.32 (m, 2H), 5.12 (s, 2H), 5.17-5.19 (m, 1H), 6.30 (bs, 1H) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 29.91 ppm; MS (m/z) 584 $[\text{M}+\text{H}]^+$.

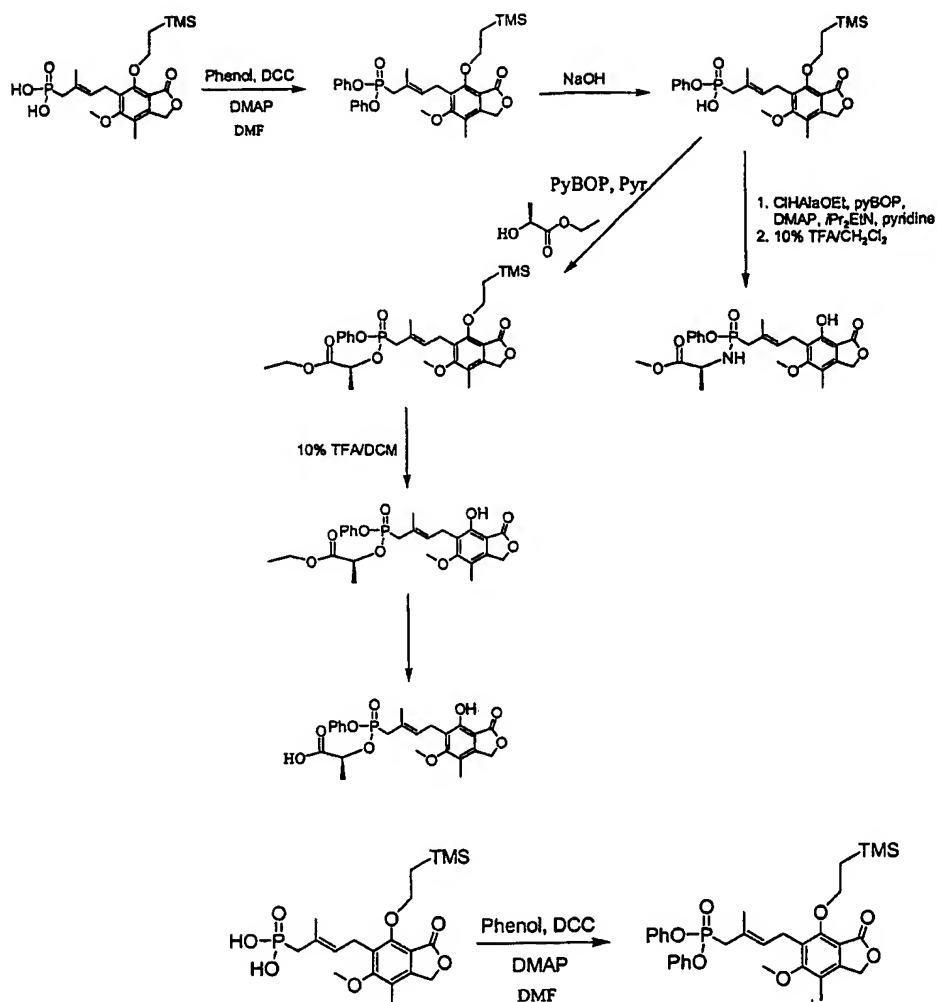


{2-[6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methyl-hex-4-enoylamino]-ethyl}-phosphonic acid

To a solution of (2-{6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilanyloxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoylamino}-ethyl)-phosphonic acid diethyl ester (36.6 mg, 0.063 mmol) in acetonitrile (1 mL) was added TMSBr (81 μ L, 0.63 mmol) followed by 2,6-lutidine (73 μ L, 0.63 mmol). The reaction was allowed to proceed overnight, when it was completed as judged by LCMS. The reaction mixture was quenched with MeOH and concentrated to dryness. The residue was purified by preparative reverse-phase HPLC to afford 5.8 mg (29%) of desired product as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 1.80 (s, 3H), 2.14 (m, 5H), 2.25 (m, 4H), 3.35 (m, 2H), 3.38-3.38 (m, 2H), 3.75 (s, 3H), 5.23 (s, 3H) ppm; ^{31}P (121.4 MHz, CD_3OD) δ 26.03 ppm; MS (m/z) 426 $[\text{M}-\text{H}]^-$, 428 $[\text{M}+\text{H}]^+$.

Example 282: Preparation of Representative Compounds of the Invention.

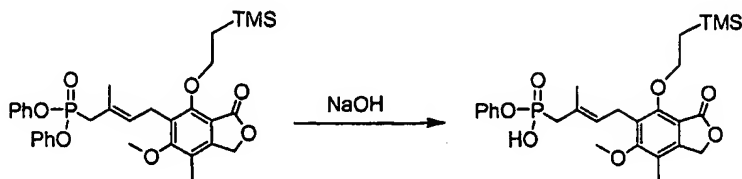
Representative compounds of the invention can be prepared as illustrated below.



5 **{4-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-phosphonic acid diphenyl ester**

To a solution of [4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl]-phosphonic acid (260 mg, 0.59 mmol) in DMF (6 mL) and phenol (555 mg, 5.9 mmol) was added
 10 dicyclohexyl carbodiimide (1.21 g, 5.9 mmol) and DMAP (36 mg, 0.295 mmol). The reaction mixture was heated to 140°C for 30 minutes. After cooling to room temperature, the mixture was partitioned between EtOAc/Hexane (1:1) and 5% aqueous LiCl solution. The organic layer was washed with 5% aqueous LiCl solution repeatedly, then dried over Na_2SO_4 . After removal of solvent, the

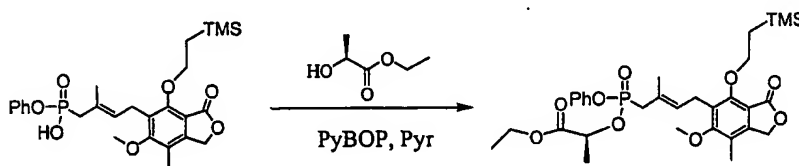
residue was purified by silica gel chromatography to provide 75 mg (21%) of the desired product. MS (m/z) 617 [$M+Na$] $^+$.



5

{4-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-phosphonic acid monophenyl ester

To a solution of {4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-phosphonic acid
 10 diphenyl ester (75 mg, 0.126 mmol) in THF (5 mL) was added 1N NaOH (0.1 mL) solution. The mixture was allowed to stir at room temperature for 16 hours. EtOAc was added and the resulting mixture was washed with 1H HCl. The organic layer was concentrated to dryness and the residue was purified by RP
 15 HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 24.8 mg (38 %) of the desired product. MS (m/z) 517 [$M-H$] $^-$, 541 [$M+Na$] $^+$.



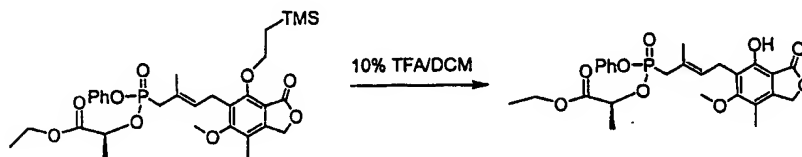
20

2-({4-[6-Methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-phenoxy-phosphinoyloxy)-propionic acid ethyl ester

To a solution of {4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-phosphonic acid
 25 monophenyl ester (25 mg, 0.048 mmol) and ethyl (S)-(-)-lactate (34 mg, 0.288 mmol) in pyridine (1 mL) was added PyBOP (125 mg, 0.24 mmol). The

solution was stirred at room temperature for 16 hours and concentrated. The residue was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 24 mg (83%) of the desired product. MS (*m/z*) 641 [M+Na]⁺.

5



2-([4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyl]-phenoxy-phosphinoyloxy)-propionic acid ethyl ester

10 ester

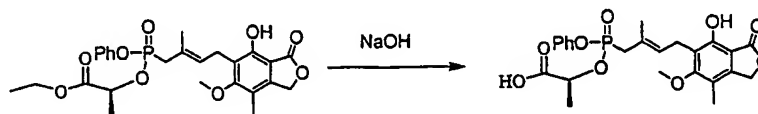
To a solution of 2-([4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl]-phenoxy-phosphinoyloxy)-propionic acid ethyl ester (24 mg, 0.039 mmol) in DCM (1 mL) was added TFA (0.5 mL) and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was dried under reduced pressure and the residue was purified by RP-HPLC to provide 18 mg (90%) of the desired product as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ 1.18-1.34 (m, 3H), 1.36-1.48 (dd, 3H), 2.02 (m, 3H), 2.17 (s, 3H), 2.78-2.98 (dd, 2H), 3.45 (m, 2H), 3.79 (s, 3H), 4.05-4.25 (m, 2H), 4.97 (m, 1H), 5.21 (s, 2H), 5.48 (t, *J* = 7.2 Hz, 1H), 7.05-7.18 (m, 5H) ppm; ³¹P (121.4 MHz, CDCl₃) δ 24.59, 26.13 ppm; MS (*m/z*) 517 [M-H]⁻, 519 [M+H]⁺.

20

Example 283: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.

25

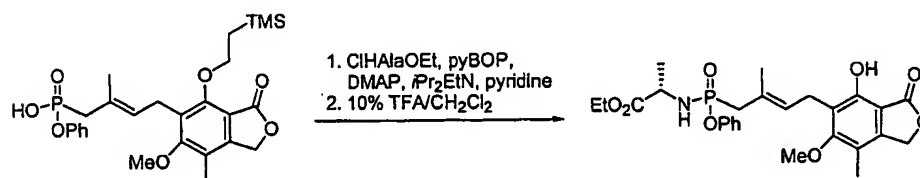


2-[[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyl]-phenoxy-phosphinoyloxy}-propionic acid

To a solution of 2-[[4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyl]-phenoxy-phosphinoyloxy}-propionic acid ethyl ester (10 mg, 0.019 mmol) in THF (3 mL) was added 1N NaOH (232 μ L), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was dried under reduced pressure and the residue was purified by RP-HPLC to provide 6 mg (77 %) of the desired product as a clear oil. ^1H NMR (300 MHz, CD_3OD) δ 1.41 (d, $J = 7$ Hz, 3H), 1.97 (s, 3H), 2.16 (s, 3H), 2.59 (d, $J = 22$ Hz, 2H), 3.45 (m, 2H), 3.79 (s, 3H), 4.83 (m, 1H), 5.26 (s, 2H), 5.43 (t, $J = 7.2$ Hz, 1H) ppm; ^{31}P (121.4 MHz, CD_3OD) δ 27.02 ppm; MS (m/z) 413 $[\text{M}-\text{H}]^-$, 415 $[\text{M}+\text{H}]^+$.

Example 284: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.



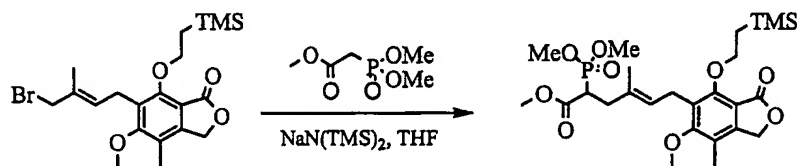
2-[[4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyl]-phenoxy-phosphinoylamino}-propionic acid ethyl ester

{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl}-phosphonic acid monophenyl ester (1 g, ~ 1.9 mmol) was combined with pyBOP (2 g, 4 mmol) and DMAP (120 mg, 0.96 mmol). A solution of L-alanine ethyl ester hydrochloride salt (2.9 g, 19 mmol) and diisopropylethylamine (6.7 mL, 38 mmol) in pyridine (5 mL) was added to the monoacid mixture and the reaction was stirred at room temperature for 12 hours. The reaction mixture was then concentrated and

purified twice by column chromatography (1% MeOH/CH₂Cl₂ 3% MeOH/CH₂Cl₂). The resulting oil was dissolved in a vigorously-stirred solution of 10% TFA/CH₂Cl₂ (30 mL) at -40°C. The reaction was gradually warmed to 0°C. After about 3 hours, the reaction was complete. Pyridine (4.5 mL) was added, and the reaction mixture was concentrated. The product was purified by preparative TLC (5% MeOH/CH₂Cl₂) and concentrated to give 210 mg (21%) of the desired product as a light yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.83-7.70 (m, 1H), 7.30-7.20 (m, 2H), 7.18-7.03 (m, 3H), 5.60-5.35 (m, 1H), 5.21 (s, 2H), 4.17-3.95 (m, 3H), 3.79 (s, 3H), 3.60-3.40 (m, 3H), 2.80-2.60 (m, 2H), 2.17 (m, 3H), 2.01 (m, 3H), 1.30-1.10 (m, 6H) ppm; ³¹P NMR (121 MHz, CDCl₃) δ 28.0, 27.5 ppm; MS (*m/z*) 516 [M-H]⁻.

Example 285: Preparation of Representative Compounds of the Invention.

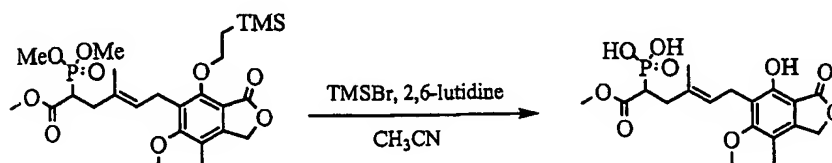
Representative compounds of the invention can be prepared as illustrated below.



2-(Dimethoxy-phosphoryl)-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid methyl ester

To a solution of trimethylphosphonoacetate (63 μL, 0.39 mmol) in THF (1 mL) was added NaN(TMS)₂ (0.39 mmol, 0.39 mL) at ambient temperature. After 30 minutes, a solution of 6-(4-bromo-3-methyl-but-2-enyl)-5-methoxy-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one (69 mg, 0.156 mmol) in THF (1 mL) was added. The reaction mixture was stirred for 2 hours, when a precipitate was observed. The reaction mixture was worked up by addition of a saturated aqueous solution of ammonium chloride and extraction of the product with EtOAc. The organic extract was dried and the product was purified using silica gel chromatography with 0-100% EtOAc-Hexanes to

provide 40 mg of the desired product as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 0.05 (s, 9H), 1.20- 1.26 (m, 2H), 1.79 (s, 3H), 2.17 (s, 3H), 2.42- 2.72 (m, 2H), 3.19 (ddd, 1H, $J=4, 12, 23$ Hz), 3.39 (d, 2H, $J=7$ Hz), 3.62 (s, 3H), 3.75 (s, 3H), 3.77- 3.84 (m, 6H), 4.27- 4.34 (m, 2H), 5.12 (s, 2H), 5.24 (t, 1H, $J=7$ Hz) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 25.1 ppm; MS (m/z) 565.2 [$\text{M}+\text{Na}$] $^+$.



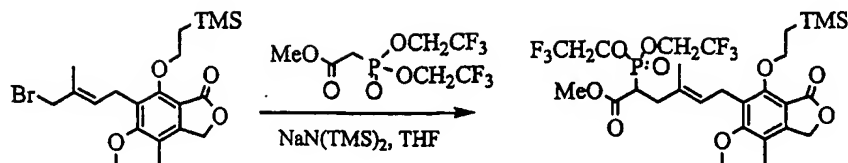
6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-

4-methyl-2-phosphono-hex-4-enoic acid methyl ester

To a solution of 2-(dimethoxy-phosphoryl)-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid methyl ester (30 mg, 0.055 mmol) in acetonitrile (2 mL) was added trimethylsilyl bromide (0.18 mL). After 10 minutes, 2,6-lutidine (0.16 mL) was added to the reaction at ambient temperature. The reaction was allowed to proceed for 16 hours before it was concentrated to dryness. The residue was resuspended in a solution of DMF: H_2O (8: 2, 1 mL) and purified by RP HPLC using a C18 column with a gradient of H_2O , 0.1% TFA-acetonitrile, 0.1% TFA to provide 18 mg of the product as a white powder. ^1H NMR (300 MHz, CD_3OD) δ 1.81 (s, 3H), 2.16 (s, 3H), 2.40-2.49 (m, 1H), 2.63 (dt, 1H, $J=6, 17$ Hz), 3.07 (ddd, 1H, $J=4, 12, 23$ Hz), 3.38 (3, 2H, $J=7$ Hz), 3.52 (s, 3H), 3.77 (s, 3H), 5.25 (s, 2H), 5.28 (t, 1H, $J=7$ Hz) ppm; ^{31}P (121.4 MHz, CDCl_3) δ 19.5 ppm; MS (m/z) 415.2 [$\text{M}+\text{H}$] $^+$, 437.2 [$\text{M}+\text{Na}$] $^+$.

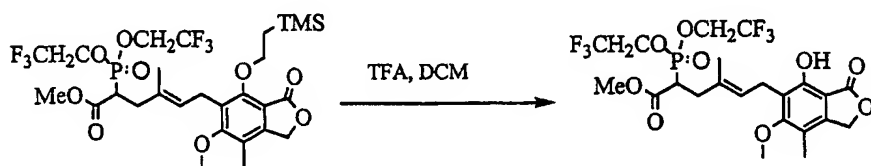
Example 286: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.



2-(Bis-(2,2,2-trifluoroethoxy)phosphoryl)-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid methyl ester

To a solution of [bis-(2,2,2-trifluoro-ethoxy)-phosphoryl]-acetic acid methyl ester (186 μ L, 0.88 mmol) in anhydrous THF (2 mL) was added a solution of 1N $\text{NaN}(\text{TMS})_2$ in THF (0.88 mL, 0.88 mmol). The solution was stirred at room temperature for 30 minutes, whereupon a solution of 6-(4-bromo-3-methyl-but-2-enyl)-5-methoxy-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one (98 mg, 0.22 mmol) in THF (1 mL) was added. The reaction mixture was stirred overnight when a precipitate was observed. The reaction mixture was worked up by addition of a saturated aqueous solution of ammonium chloride and extraction of the product with EtOAc. The organic extract was dried and the product was purified by RP HPLC using a C18 column with a gradient of H_2O , 0.1% TFA-acetonitrile, 0.1% TFA to provide 72 mg (48%) of the product as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 0.05 (s, 9H), 1.22 (t, 3H, $J = 7$ Hz), 1.81 (s, 3H), 2.18 (s, 3H), 2.5- 2.7 (m, 2H), 3.3 (ddd, 1H, $J = 4, 12, 23$ Hz), 3.40 (d, 2H, $J = 7$ Hz), 3.65 (s, 3H), 3.76 (s, 3H), 4.29- 5.13 (m, 6H), 5.13 (s, 2H), 5.28 (t, 1H, $J = 7$ Hz) ppm; MS (m/z) 701.2 $[\text{M}+\text{Na}]^+$.



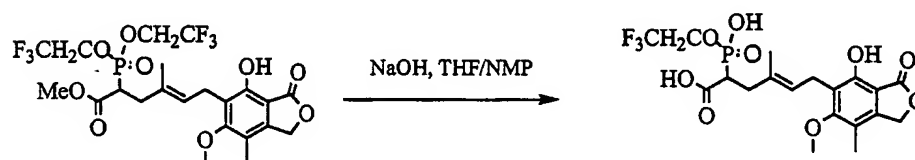
2-(Bis-(2,2,2-trifluoroethoxy)phosphoryl)-6-[6-methoxy-7-methyl-3-oxo-4-(2-hydroxyoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid methyl ester

[2-(Bis-(2,2,2-trifluoroethoxy)phosphoryl)-6-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-4-methyl-hex-4-enoic acid methyl ester (70 mg) was dissolved in a solution of 10% trifluoroacetic acid in dichloromethane (5mL). After 10 minutes, the mixture
 5 was concentrated and the product was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 45 mg (75%) of the product as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 1.81 (s, 3H), 2.16 (s, 3H), 2.5- 2.7 (m, 2H), 3.3 (ddd, 1H), 3.38 (d, 2H, *J*= 7 Hz), 3.65 (s, 3H), 3.77 (s, 3H), 4.33- 4.43 (m, 4H), 5.21 (s, 2H), 5.33 (t, 1H, *J*= 7 Hz) ppm;
 10 ³¹P (121.4 MHz, CDCl₃) δ 25.8 ppm; MS (*m/z*) 601.2 [M+Na]⁺.

Example 287: Preparation of Representative Compounds of the Invention.

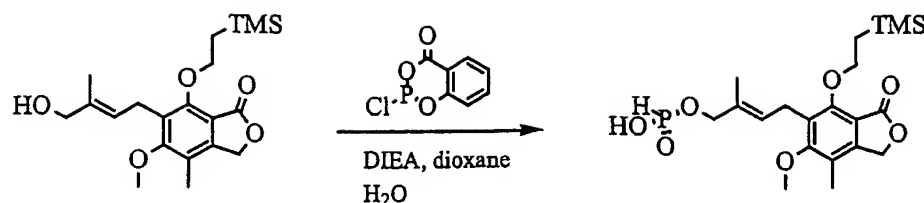
Representative compounds of the invention can be prepared as illustrated below.

15



6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-[hydroxy-(2,2,2-trifluoro-ethoxy)-phosphoryl]-4-methyl-hex-4-enoic acid

20 To a solution of [bis-(2,2,2-trifluoro-ethoxy)-phosphoryl]-acetic acid methyl ester (186 μL, 0.88 mmol) in anhydrous THF (0.5 mL) was added a solution of 1N NaOH (aqueous; 0.06 mL) and N-methylpyrrolidinone (0.2mL). After 6.5 hours, another aliquot of 1N NaOH (0.06mL) was added and the mixture was stirred overnight. After concentration, the residue was suspended in
 25 DMF (<1mL), neutralized with a few drops of TFA and purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, 0.1% TFA to provide 5.6 mg (72%) of the product as a white powder after lyophilization. ¹H NMR (300 MHz, CD₃OD) δ 1.83 (s, 3H), 2.16 (s, 3H), 2.43-2.51 (m, 1H), 2.59-2.70 (m, 1H), 3.13 (ddd, 1H), 3.40 (d, 2H), 3.76 (s, 3H), 4.36-4.47 (m, 2H),
 30 5.25 (s, 2H), 5.34 (t, 1H, *J*= 7 Hz) ppm; MS (*m/z*) 505.2 [M+Na]⁺.

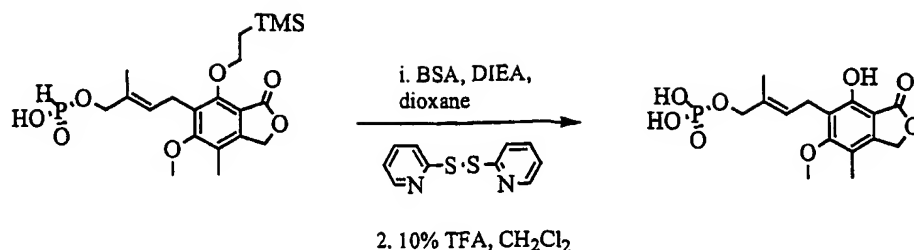


Example 288: Preparation of Representative Compounds of the Invention.

Representative compounds of the invention can be prepared as illustrated below.

Phosphorous acid mono-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl} ester

To a solution of 6-(4-hydroxy-3-methyl-but-2-enyl)-5-methoxy-4-methyl-7-(2-trimethylsilyl-ethoxy)-3H-isobenzofuran-1-one (75 mg, 0.20 mmol) and DIEA (49 μ L, 0.28 mmol) in dioxane (2 mL) was added 2-chloro-4H-1,3,2-benzodioxaphosphorin-4-one (56.7 mg, 0.28 mmol) according the procedure of Shadid, B. et al., *Tetrahedron*, **1989**, *45*, 12, 3889. After 10 minutes, another portion of 2-chloro-4H-1,3,2-benzodioxaphosphorin-4-one (40 mg, 0.20 mmol) and DIEA (35 μ L, 0.20 mmol) were added. The reaction was allowed to proceed at room temperature for an additional hour, after which it was quenched by the addition of H₂O. The solution was stirred for another 10 minutes and concentrated *in vacuo* to a small volume. The product was triturated with diethyl ether and coevaporated from acetonitrile (4 x 10 mL) to provide the product. ¹H NMR (300 MHz, CDCl₃) δ 0.03 (s, 9H), 1.08- 1.30 (m, 2H), 1.84 (br s, 3H), 2.17 (s, 3H), 3.46 (br s, 2H), 3.76 (s, 3H), 4.21- 4.39 (m, 4H), 5.12 (s, 2H), 5.43- 5.60 (m, 1H), 7.83 (br s, 1H); ³¹P (121.4 MHz, CDCl₃) δ 7.22; MS (*m/z*) 441 [M-H]⁺.



Example 289: Preparation of Representative Compounds of the Invention.

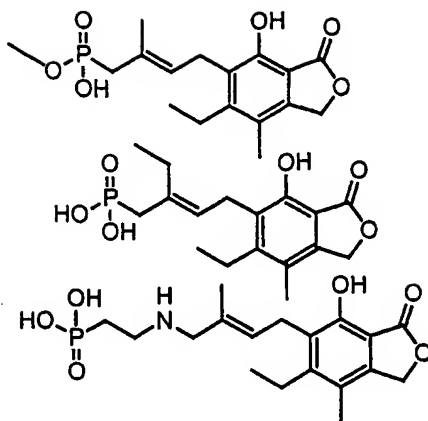
Representative compounds of the invention can be prepared as illustrated
5 below.

Phosphoric acid mono-{4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl} ester

A solution of phosphorous acid mono-{4-[6-methoxy-7-methyl-3-oxo-4-
10 (2-trimethylsilylanyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enyl} ester (27 mg, 0.06 mmol) in dioxane (1 mL) was stirred with DIEA (21 μ L, 0.12 mmol) and N,O-bis(trimethylsilyl)acetamide (29 μ L, 0.12 mmol) at room temperature for 3 hours. To the reaction solution was added 2,2'-
15 dipyridyldisulfide (16 mg, 0.072 mmol) and the mixture was allowed to stir for an additional 2 hours at room temperature. The reaction mixture was diluted by addition of H₂O and the solution was stirred for 2 more hours when it was concentrated. The residue was dissolved in a solution of 10% TFA/ CH₂Cl₂ and stirred at room temperature for 9 hours. The reaction mixture was dried under reduced pressure and the product was purified by reverse-phase HPLC to
20 provide the desired product as a white solid. ¹H NMR (300 MHz, CD₃OD) δ 1.87 (s, 3H), 2.16 (s, 3H), 3.47 (d, 2H, J = 7 Hz), 3.79 (s, 3H), 4.28 (d, 2H, J = 6 Hz), 5.26 (s, 2H), 5.50- 5.61 (m, 1H); ³¹P (121.4 MHz, CD₃OD) δ 0.50; MS (m/z) 357 [M-H]⁻.

25 Example 290: Specific Embodiments of the Invention

Several compounds of the invention are presented below.



Example 291: Preparation of Representative Compounds of the Invention

Additional representative compounds of the invention, and intermediates thereof, can be prepared according to the methods presented below.



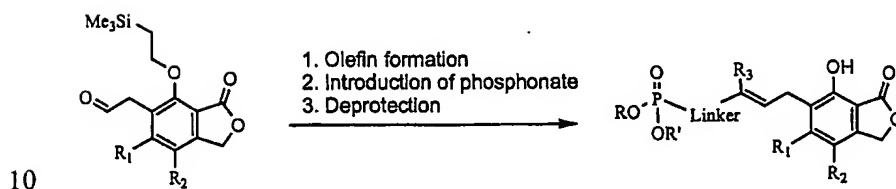
Linker = 0-8 atoms, preferably 1-6;

R₁ = OMe, OEt, vinyl, Et, cyclopropyl, NHMe, NHCHO

R₂ = Me, Cl, CF₃

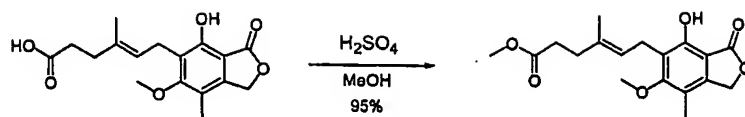
R₃ = H, Me, cyclopropyl, Et, vinyl, CF₃

R₄ = H, Cl, Me, Et, cyclopropyl, vinyl, allyl,

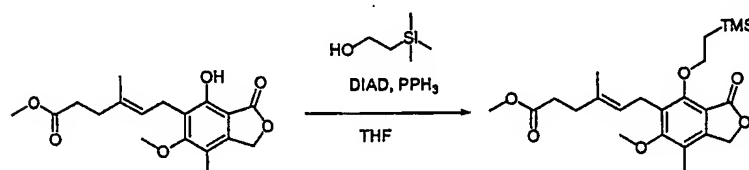


Synthesis of phenacetaldehydes with variants at R₁, R₂

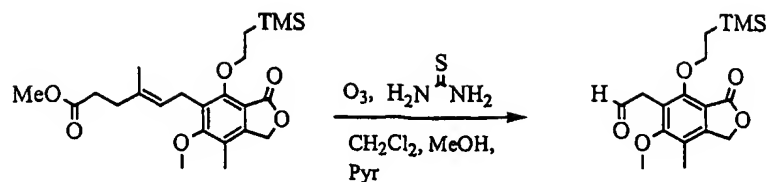
The parent compound (R₁ = OMe; R₂ = Me) is accessible by semi-synthesis from mycophenolic acid as follows:



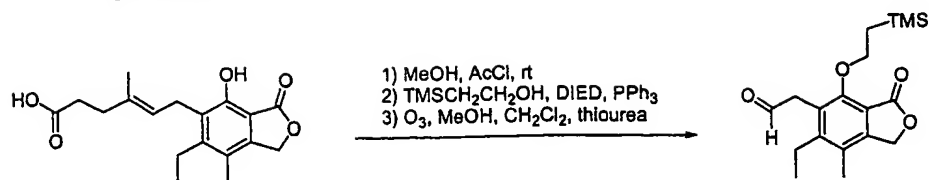
- To a solution of mycophenolic acid (500 g, 1.56 mol) in MeOH (4 L) under nitrogen atmosphere was added sulfuric acid (10 mL) dropwise, and the suspension was stirred at room temperature. After 2 hours, the reaction became homogeneous, and soon thereafter a precipitate was formed. The reaction was allowed to stir at room temperature for 10 hours, at which time TLC indicated complete reaction. The reaction was cooled in an ice bath to 10°C and then filtered using a Buchner funnel. The filter cake was washed with ice cold methanol (750 mL) followed by hexanes (750 mL) and then dried to give 497 g (95%) of the desired product as a solid: ¹H NMR (300 MHz, CDCl₃) δ, 1.81 (s, 3H), 2.18 (s, 3H), 2.15 (s, 3H), 2.37- 2.50 (m, 4H), 3.38 (d, 2H, *J*= 7 Hz), 3.62 (s, 3H), 3.77 (s, 3H), 5.13 (s, 2H), 5.22 (m, 1H), 7.17 (s, 1H).



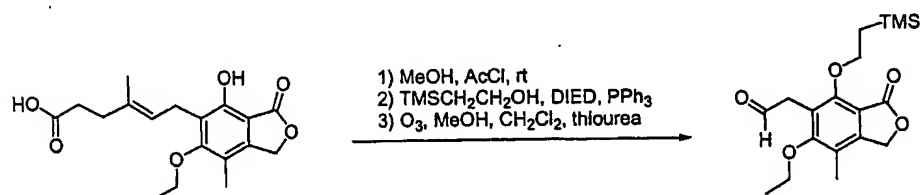
- To a solution (3.99 g, 11.9 mmol), PPh₃ (4.68 g, 17.9 mmol), and diisopropyl azodicarboxylate (3.46 mL, 17.9 mmol) in THF (60 mL) at 0°C was added a solution of 2-trimethylsilylethanol (2.05 mL, 14.3 mmol) in THF (20 mL). The resulting yellow solution was allowed to warm to room temperature and stirred for 4 hours. The reaction was worked up by concentrating the solution to dryness and addition of ether and hexanes. Triphenylphosphine oxide was removed by filtration and the filtrate was concentrated and purified by silica gel chromatography to provide 4.8 g (100%) as a clear oil: ¹H NMR (300 MHz, CDCl₃) δ 0.03 (s, 9H), 1.18- 1.30 (m, 2H), 1.81 (s, 3H), 2.18 (s, 3H), 2.25- 2.33 (m, 2H), 2.37- 2.45 (m, 2H), 3.42 (d, 2H, *J*= 7 Hz), 3.62 (s, 3H), 3.77 (s, 3H), 4.25- 4.35 (m, 2H), 5.13 (s, 2H), 5.12- 5.22 (m, 1H).



A solution (9.6 g, 22 mmol) in MeOH (90 mL), CH₂Cl₂ (90 mL) and
 5 pyridine (0.7 mL) was cooled to -70°C using a dry ice/ acetone bath. A stream
 of ozone was bubbled through the reaction *via* a gas dispersion tube until the
 reaction became blue in color (1.5 hours). The ozone line was replaced with a
 stream of nitrogen and bubbling continued for another 30 minutes, by which
 time the blue color had disappeared. To this solution at -70°C was added
 10 thiourea (1.2 g, 15.4 mmol) in one portion, and the cooling bath was removed.
 The reaction was allowed to warm to room temperature and stirred for 15 hours.
 The reaction was worked up by filtration to remove solid thiourea S-dioxide, and
 then partitioned between CH₂Cl₂ and water. The organic layer was removed.
 The aqueous layer was washed with CH₂Cl₂ and the organic extracts were
 15 combined, washed with aqueous 1N HCl, saturated NaHCO₃ and brine, and
 dried *in vacuo*. The residue was purified by silica gel chromatography to afford
 7.3 g (99 %) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ -0.01 (s, 9H), 1.05-
 1.15 (m, 2H), 2.15 (s, 3H), 3.69 (s, 3H), 3.78 (d, 2H, $J=1$ Hz), 4.27- 4.39 (m,
 2H), 5.11 (s, 2H), 9.72 (d, 1H, $J=1$ Hz).

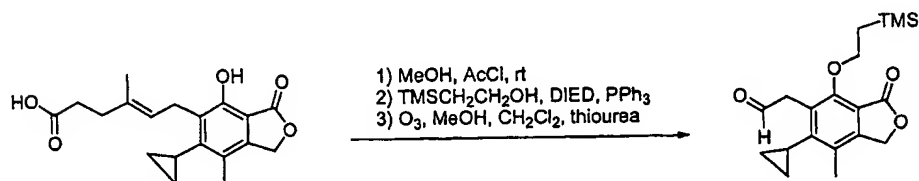
R₁ variants

- 5 The starting material, synthesized according to *J. Med. Chem.*, **1996**, *39*, 4181-4196, is transformed to the desired aldehyde using methods analogous to those described above.



10

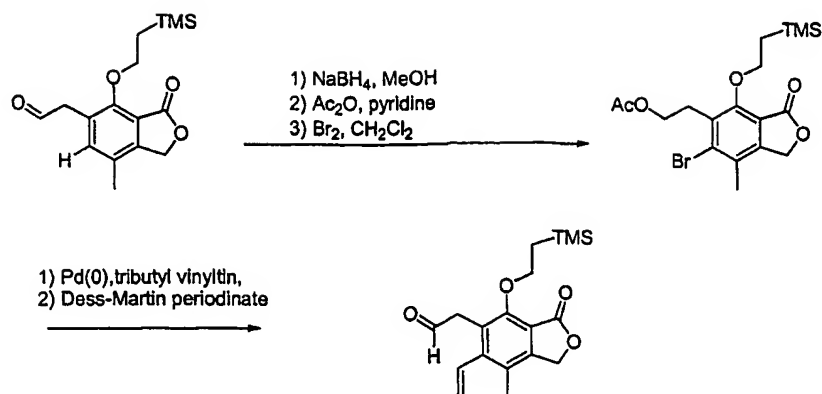
- The starting material, synthesized according to *J. Med. Chem.*, **1996**, *39*, 4181-4196, is transformed to the desired aldehyde using methods analogous to those described above.



15

- The starting material, synthesized according to *J. Med. Chem.*, **1996**, *39*, 4181-4196, is transformed to the desired aldehyde using methods analogous to those described above.

20



The aldehyde is dissolved in an organic solvent such as methanol and sodium borohydride is added. At the end of the reaction, aqueous HCl solution is added and the solvent is removed *in vacuo*. Further purification is achieved by chromatography.

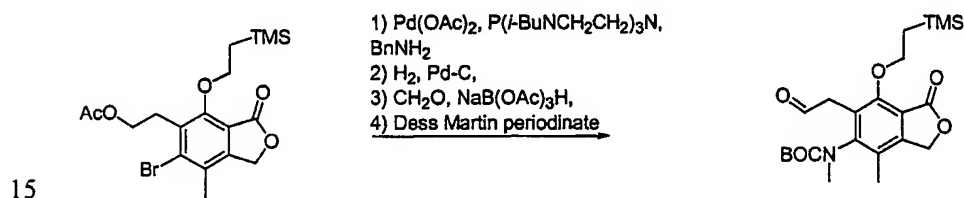
The resulting alcohol is dissolved in an organic solvent such as dichloromethane (DCM). Pyridine and acetic anhydride are added and stirring at room temperature is continued. At the end of the reaction additional DCM is added and the solution is washed with aqueous HCl solution, aqueous sodium bicarbonate solution, and dried over sodium sulfate. Filtration and evaporation of the solvent *in vacuo* gives the crude product. Further purification is achieved by chromatography.

The acetate is dissolved in DCM and bromine is added, according to a procedure from *J. Med. Chem.*, 1996, 39, 4181-4196. At the end of the reaction, additional DCM is added and the solution is washed with aqueous sodium thiosulfate solution and brine. The organic layer is dried over sodium sulfate. Filtration and evaporation of solvents yields the crude material. Further purification is achieved by chromatography.

The product of the previous step, lithium chloride, triphenylarsine, tributylvinyltin, and tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct are heated in an organic solvent such as *N*-methylpyrrolidinone at an elevated temperature of approximately 55°C, according to a procedure from *J. Med. Chem.*, 1996, 39, 4181-4196. At the end of the reaction, the mixture is cooled to room temperature and poured into a mixture of ice, potassium fluoride,

water, and ethyl acetate. Stirring is continued for one hour. The suspension is filtered through Celite and extracted with ethyl acetate. The combined organic extracts are dried over sodium sulfate. The solvents are removed *in vacuo* and the crude material is further purified by chromatography.

- 5 The product of the previous step is dissolved in an organic solvent such as DCM or THF. 1,1,1-tris(acyloxy)-1,1-dihydro-1,2benziodoxol-3-(1H)-one (Dess-Martin reagent) is added and the solution is stirred at room temperature, according to a procedure from *J. Org. Chem.*, **1984**, *48*, 4155-4156. At the end of the reaction diethyl ether is added, followed by aqueous sodium hydroxide
10 solution. The layers are separated and the organic layer is washed with aqueous sodium hydroxide solution, water, and dried over sodium sulfate. Filtration and evaporation of solvents yields the crude product. Further purification is achieved by chromatography.



- The starting material is dissolved in an organic solvent such as toluene. P(*isobutyl*NCH₂CH₂)₃N, palladium(II)acetate, sodium *tert.* butoxide, and benzylamine are added and the mixture was heated at 80°C, according to a
20 procedure from *J. Org. Chem.*, **2003**, *68*, 452-459. At the end of the reaction, the mixture is cooled to room temperature and the solvents are removed *in vacuo*. The crude material is purified by chromatography. Any residual acetate is removed by brief treatment with methanolic sodium methoxide.

- The benzyl-protected aniline is dissolved in an organic solvent such as
25 DMF. Palladium on carbon is added and the reaction mixture is placed under an atmosphere of hydrogen. At the end of the reaction, the mixture is filtered through Celite. The solvents are removed *in vacuo*. Further purification is achieved by chromatography.

The resulting primary aniline is dissolved in an organic solvent such as THF, acetonitrile, or DMF and is treated with formaldehyde and sodium triacetoxyborohydride as described in *J. Org. Chem.*, 1996, 61, 3849-3862. The reaction is quenched with aqueous sodium bicarbonate and the product is
 5 extracted with an organic solvent such as ethyl acetate. The crude material is treated with di-*t*-butyl dicarbonate in an organic solvent such as dimethylformamide and aqueous sodium hydroxide. The resulting carbamate is purified by chromatography.

The primary alcohol product is dissolved in an organic solvent such as
 10 DCM or THF. 1,1,1-tris(acyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (Dess-Martin reagent) is added and the solution is stirred at room temperature, according to a procedure from *J. Org. Chem.*, 1984, 48, 4155-4156. At the end of the reaction diethyl ether is added, followed by aqueous sodium hydroxide solution. The layers are separated and the organic layer is washed with aqueous
 15 sodium hydroxide solution, water, and dried over sodium sulfate. Filtration and evaporation of solvents yields the crude product. Further purification is achieved by chromatography.



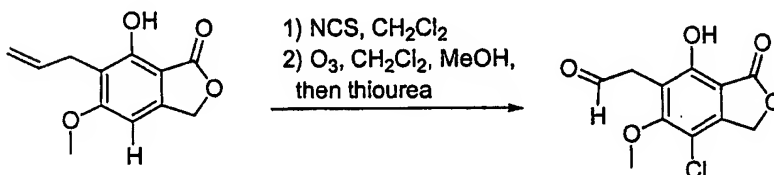
20

The starting material is dissolved in an organic solvent such as DCM or THF and is treated with the mixed anhydride of formic and pivalic acids, according to a procedure from *Recl. Trav. Chem. Pay-Bas*, 1982, 101, 460. At the end of the reaction, the solvent and all volatiles are removed *in vacuo* and the
 25 crude product is further purified by chromatography.

The product is dissolved in an organic solvent such as DCM or THF. 1,1,1-Tris(acyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (Dess-Martin reagent) is added and the solution was stirred at room temperature, according to a procedure from *J. Org. Chem.*, 1984, 48, 4155-4156. At the end of the

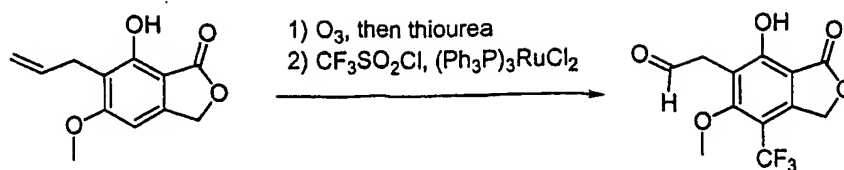
reaction diethyl ether is added, followed by aqueous sodium hydroxide solution. The layers are separated and the organic layer is washed with aqueous sodium hydroxide solution, water, and dried over sodium sulfate. Filtration and evaporation of solvents yields the crude product. Further purification is achieved by chromatography.

R₂ variants



The starting material is dissolved in an organic solvent such as DMF and reacted with *N*-chlorosuccinimide, according to a procedure from *J. Med. Chem.*, 1996, 39, 4181-4196. After the starting material is consumed the reaction mixture is poured into water and the product is extracted with diethyl ether. The combined organic layers are dried over sodium sulfate. Filtration and evaporation of the solvent yields a crude reaction product.

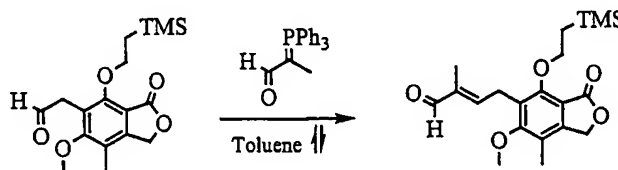
The product of step one is dissolved in a mixture of organic solvents such as methanol, DCM, and pyridine. The solution is cooled to -78°C and ozone is bubbled into the solution until a blue color persists. The excess ozone is removed with a nitrogen stream. The reaction mixture is warmed to room temperature and thiourea is added. Stirring at room temperature is continued. The reaction mixture is filtered and partitioned between DCM and water. The aqueous layer is extracted with DCM and the combined organic layers are washed with HCl (1 N), saturated aqueous sodium bicarbonate solution and brine. The solution is dried over sodium sulfate. Filtration and evaporation of the solvents yields the crude aldehyde. Further purification is achieved by chromatography.



The starting material is dissolved in a mixture of organic solvents such as methanol, DCM, and pyridine. The solution is cooled to -78°C and ozone is bubbled into the solution until a blue color persists. The excess ozone is removed with a nitrogen stream. The reaction mixture is warmed to room temperature and thiourea is added. Stirring at room temperature is continued. The reaction mixture is filtered and partitioned between DCM and water. The aqueous layer is extracted with DCM and the combined organic layers are washed with HCl (1 N), saturated aqueous sodium bicarbonate solution, and brine. The solution is dried over sodium sulfate. Filtration and evaporation of the solvents yields the crude aldehyde. Further purification is achieved by chromatography.

The product of step one is dissolved in an organic solvent such as benzene. Trifluoromethanesulfonyl chloride and dichlorotris(triphenylphosphine)ruthenium are added and the solution is degassed. The reaction mixture is heated at 120°C , according to a procedure from *J. Chem. Soc., Perkin Trans. 1*, 1994, 1339-1346. At the end of the reaction the mixture is cooled to room temperature and the solvent is removed *in vacuo*. Further product purification is achieved by chromatography.

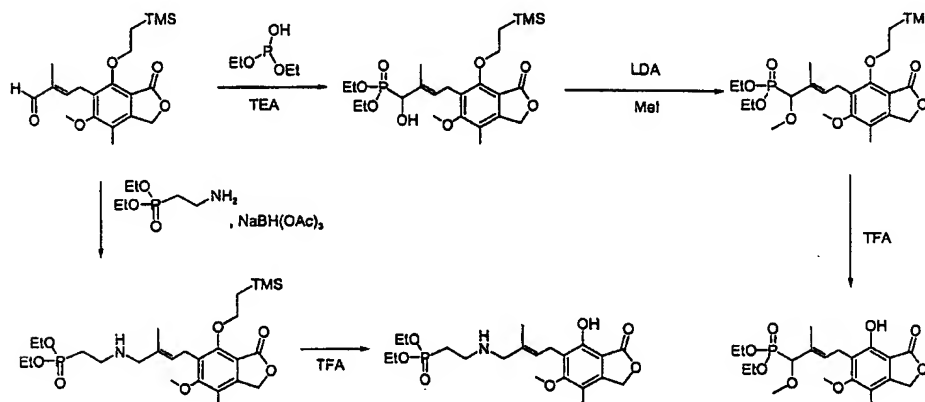
Synthesis of olefins and linkers to phosphonates



The phenacetaldehyde (5.3 g, 15.8 mmol) in toluene (50 mL) was heated at 100°C with 2-(triphenylphosphanylidene)propionaldehyde (6.8 g, 20.5 mmol) overnight. After concentration, the residue was purified by silica gel

chromatography to provide 4.24 g (72%) of the unsaturated aldehyde as a pale yellow solid. ^1H NMR (300 MHz, CDCl_3) δ 0.00 (s, 9H), 1.10- 1.21 (m, 2H), 1.87 (s, 3H), 2.16 (s, 3H), 3.67- 3.76 (m, 2H), 3.74 (s, 3H), 4.27- 4.39 (m, 2H), 5.11 (s, 2H), 6.40- 6.48 (m, 1H), 9.2 (s, 1H).

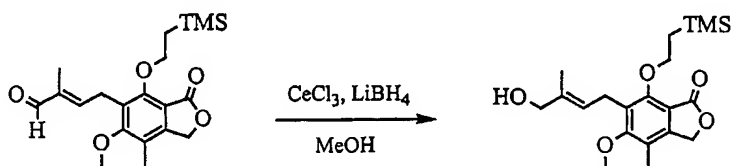
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The trimethylsilyl-protected aldehyde is treated with diethylphosphite in a solvent such as acetonitrile in the presence of a base such as triethylamine to afford the hydroxy phosphonate, according to a procedure such as that reported in *Tetrahedron*, **1995**, *51*, 2099. The hydroxy phosphonate is *O*-alkylated and then the protecting group is removed by treatment with either trifluoroacetic acid or tetrabutylammonium fluoride to generate the desired methoxy phosphonate analog.

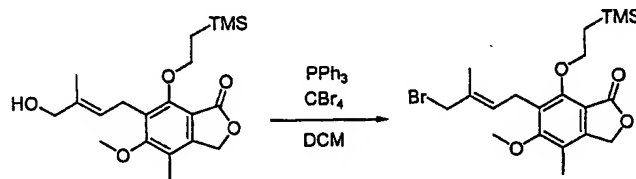
Alternatively, the aldehyde is mixed with diethyl (2-aminoethyl)phosphonate and treated with a reducing agent such as sodium triacetoxyborohydride to generate the amino phosphonate analog.

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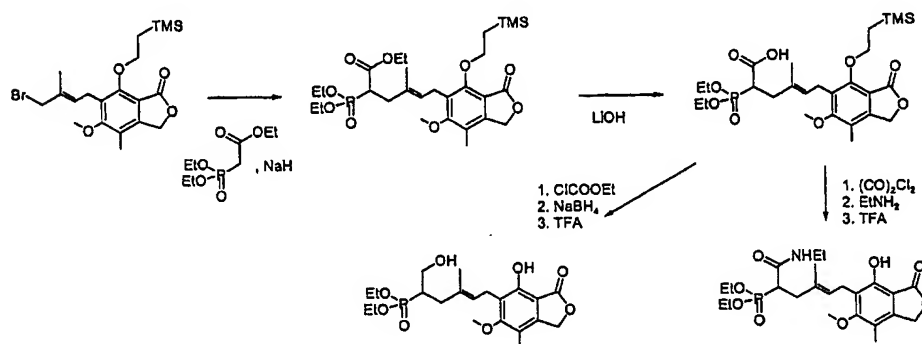
A solution of 4-[6-methoxy-7-methyl-3-oxo-4-(2-trimethylsilyl-ethoxy)-1,3-dihydro-isobenzofuran-5-yl]-2-methyl-but-2-enal (103 mg, 0.27

mmol) in methanol (5 mL) was cooled to 0°C. A solution of CeCl₃ (0.68 mL, MeOH: H₂O, 9:1) was added, followed by LiBH₄ (0.14 mL, 0.28 mmol of a 2M solution in THF). The ice bath was removed and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for an additional 40 minutes whereupon TLC indicated complete consumption of starting aldehyde. The reaction was worked up by addition of aqueous 1N HCl (0.5 mL) and the product was extracted with CH₂Cl₂. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography to provide 100 mg (97%) of the product as a clear liquid. ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 9H), 1.20 (dd, 2H, *J* = 7, 8 Hz), 1.81 (s, 3H), 2.13 (s, 3H), 3.38- 3.50 (m, 2H), 3.74 (s, 3H), 3.95 (s, 2H), 4.27 (dd, 2H, *J* = 7, 8 Hz), 5.08 (s, 2H), 5.17- 5.44 (m, 1H).

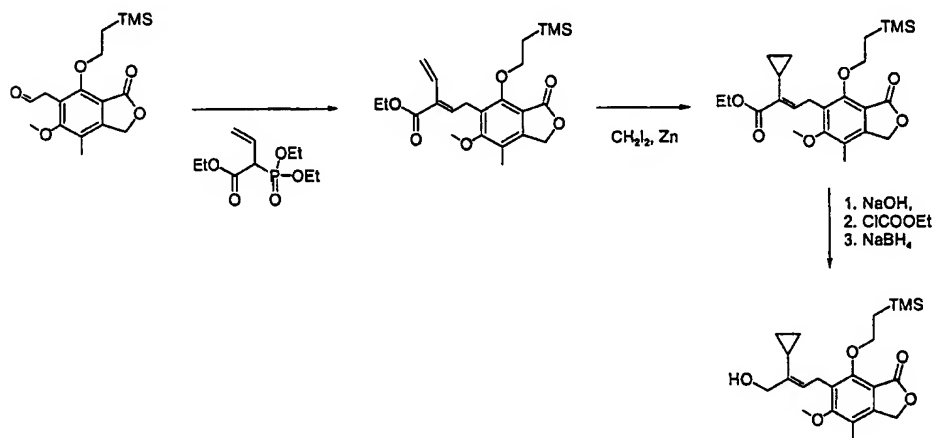


15

Polymer-supported triphenylphosphine is soaked in DCM for 1 hour. The allylic alcohol and carbon tetrabromide are sequentially added. When the reaction is complete, the mixture is filtered and the filtrate concentrated. The bromide is purified as necessary by chromatography.

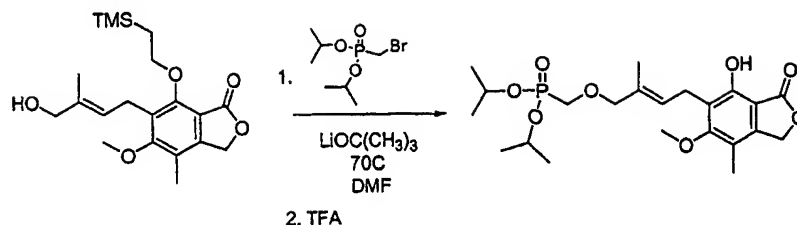


The allylic bromide is treated in an inert organic solvent such as dimethylformamide with an alkali metal salt of ethyl diethoxyphosphorylacetate (prepared by reacting ethyl diethoxyphosphorylacetate with sodium hexamethyldisilazide or sodium hydride) to afford the ethoxycarbonyl phosphonate, according to a procedure such as that described in WO 9522538. The carboxylic ester group is converted to both the carboxylic amide and the hydroxymethyl groups according to the methods conventionally utilized for amide formations and ester reductions. For example, the carboxylic ester is saponified with aqueous lithium hydroxide. The acid is activated with ethyl chloroformate and reduced with sodium borohydride to generate, after removal of the protecting group, the hydroxymethyl phosphonate analog. The acid is also converted to its acyl chloride and then reacted with ethylamine to afford the amide analog.

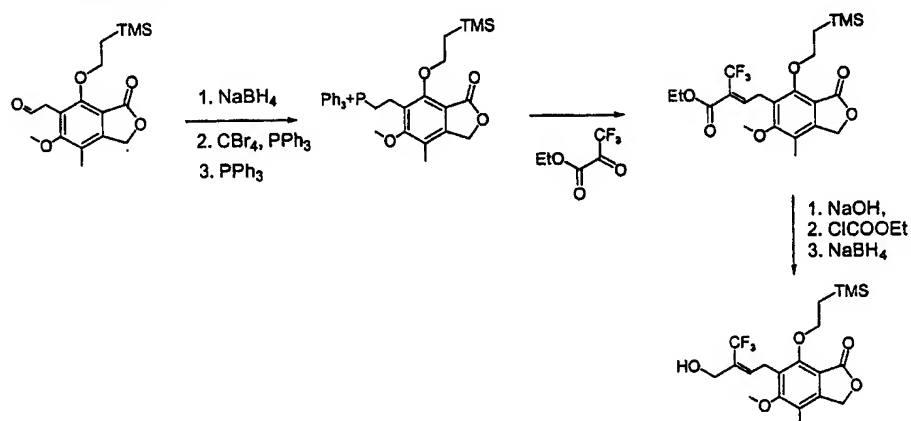


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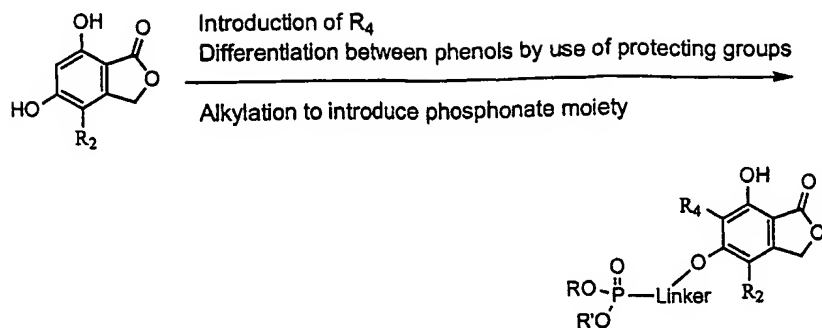
The aryl acetaldehyde is coupled with 2-(diethoxyphosphoryl)-but-3-enoic acid ethyl ester to generate the 2-vinyl substituted ester, according to a procedure such as that reported in *Synthesis*, 1999, 282. The 2-vinyl group is converted to the 2-cyclopropyl group under cyclopropanation conditions such as those described in *Tetrahedron Lett.* 1998, 39, 8621. The ester is converted to the alcohol, which, optionally, can be further subjected to reactions such as that described below to generate various phosphonate-containing mycophenolic acid analogues.



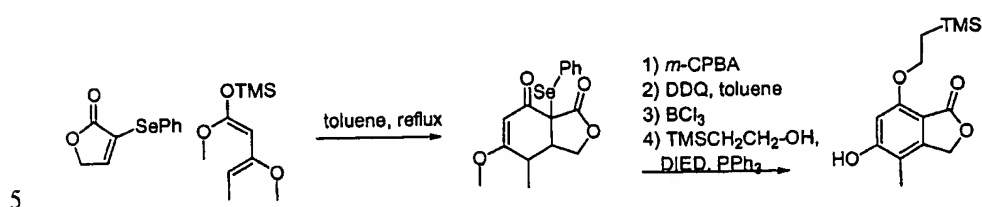
- The allylic alcohol is treated with bromomethylphosphonic acid diisopropyl ester in the presence of a base such as lithium *t*-butoxide in a solvent such as dimethylformamide. The phenol protecting group is then removed by treatment with trifluoroacetic acid.



- The phenacetaldehyde can alternatively be converted to the allyl phosphonium salt, according to a procedure such as that reported in *J. Org. Chem.* **1987**, 52, 849. The phosphonium salt is then treated with the commercially available 3,3,3-trifluoro-2-oxo-propionic acid ethyl ester and a base such as sodium hydride to generate the 2-trifluoromethyl substituted ester. The ester is converted to the alcohol, which, optionally, can be further subjected to reactions described earlier to generate mycophenolic acid analogues with various side chains containing the phosphonate group.



Introduction of R₄ variants



The enone (synthesis reviewed in *Tetrahedron*, 1985, 41, 4881-4889) and the diene (*Chem. Pharm. Bull.*, 1989, 37, 2948-2951) are dissolved in an organic solvent such as toluene, stirred at room temperature for 24 hours and heated to reflux for additional 5 hours, according to a procedure from *J. Med. Chem.*, 1996, 39, 4181-4196. The reaction mixture is cooled to room temperature and the solvent removed *in vacuo*. The crude reaction product is further purified by chromatography.

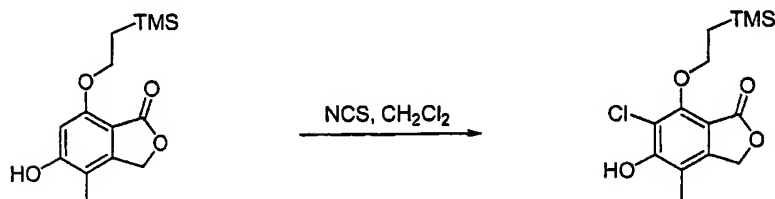
The product of step one is dissolved in an organic solvent such as DCM and *m*-chloroperbenzoic acid is added, according to a procedure from *J. Med. Chem.*, 1996, 39, 4181-4196. At the end of the reaction, the solution is poured into aqueous sodium hydrogen sulfite solution. The organic layer is washed with saturated aqueous sodium bicarbonate solution and is dried over sodium sulfate. Filtration and evaporation of solvents yields the crude product.

The crude product is dissolved in an organic solvent such as toluene and treated with dichlorodicyanoquinone (DDQ), according to a procedure from *J. Med. Chem.*, 1996, 39, 4181-4196. At the end of the reaction the solvent is removed *in vacuo* and the crude material is further purified by chromatography.

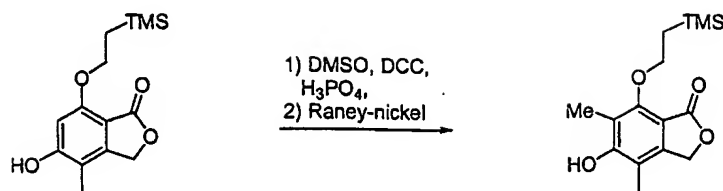
The product is dissolved in an organic solvent such as DCM and treated with boron trichloride at reflux temperature, according to a modified procedure from *J. Med. Chem.*, 1996, 39, 46-55. At the end of the reaction the solution is washed with aqueous HCl solution. The solution is dried over sodium sulfate.

- 5 Removal of the solvent yields the crude reaction product. Further purification is achieved by chromatography.

The product of the previous step and triphenylphosphine are dissolved in an organic solvent such as tetrahydrofuran (THF). Diisopropylazodicarboxylate (DIAD) is added dropwise at 0°C. Stirring is continued. A solution of 2-
10 trimethylsilyl ethanol in THF is added and stirring is continued. At the end of the reaction, the solvent is removed *in vacuo*. The crude reaction solid is extracted with a mixture of organic solvents such as hexanes and diethylether. The washings are combined and the solvents removed *in vacuo*. The desired product is further purified and separated from the undesired regioisomer by
15 chromatography.

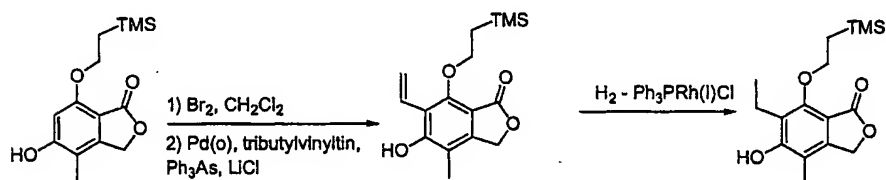


- The starting material is dissolved in an organic solvent such as
20 dimethylformamide (DMF) and reacted with *N*-chlorosuccinimide, according to a procedure from *J. Med. Chem.*, 1996, 39, 4181-4196. After the starting material is consumed the reaction mixture is poured into water and the product is extracted with diethyl ether. The combined organic layers are dried over sodium sulfate. Filtration and evaporation of the solvents yields the crude product.
25 Further purification is achieved by chromatography.



The starting material is dissolved in an organic solvent such as benzene and reacted with dimethyl sulfoxide (DMSO), dicyclohexylcarbodiimide (DCC), and orthophosphoric acid according to a procedure from *J. Am. Chem. Soc.*, 1966, 88, 5855-5866. At the end of the reaction, the suspension is filtered and the organic layer washed with aqueous sodium bicarbonate solution and dried over sodium sulfate. Filtration and evaporation of solvents yields the crude material. Further purification is achieved by chromatography.

The product of step one is dissolved in an organic solvent such as DCM or THF and treated with Raney nickel, according to procedures reviewed in *Chem. Rev.*, 1962, 62, 347-404. When all starting material is consumed, the reaction is filtered and the solvent removed *in vacuo*. Further purification is achieved by chromatography.

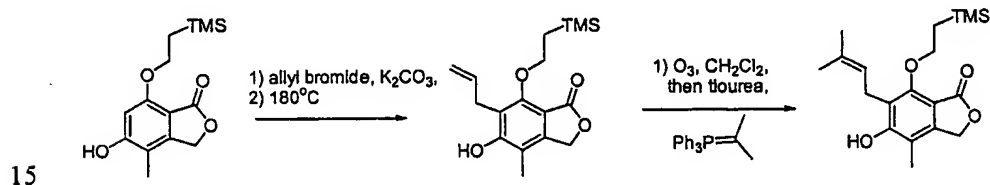


The starting material is dissolved in an organic solvent such as DCM and bromine is added, according to a procedure from *J. Med. Chem.*, 1996, 39, 4181-4196. At the end of the reaction, additional DCM is added and the solution washed with aqueous sodium thiosulfate solution and brine. The organic layer is dried over sodium sulfate. Filtration and evaporation of solvents yields the crude material. Further purification is achieved by chromatography on silica gel.

The starting material, lithium chloride, triphenylarsine, tributylvinyltin, and tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct are heated in an organic solvent such as *N*-methylpyrrolidinone at an elevated temperature of

approximately 55°C, according to a procedure from *J. Med. Chem.*, 1996, 39, 4181-4196. At the end of the reaction, the mixture is cooled to room temperature and poured into a mixture of ice, potassium fluoride, water, and ethyl acetate. Stirring is continued for 1 hour. The suspension is filtered
 5 through Celite and extracted with ethyl acetate. The combined organic extracts are dried over sodium sulfate. The solvents are removed *in vacuo* and the crude material is further purified by chromatography.

The product of step two is dissolved in a mixture of organic solvents such as benzene and ethyl acetate. Tris(triphenylphosphine)rhodium(I) chloride
 10 is added and the reaction is placed under an atmosphere of hydrogen, according to a procedure from *J. Med. Chem.*, 1996, 39, 4181-4196. The solvents are removed *in vacuo* and the crude reaction is filtered through silica gel. Further purification is achieved by chromatography.



The starting material is dissolved in an organic solvent such as DMF. Potassium carbonate and allyl bromide are added and stirring at room temperature is continued, according to a procedure from *J. Med. Chem.*, 1996,
 20 39, 4181-4196. After all the starting material is consumed, aqueous HCl solution and diethyl ether are added and the organic layer is collected and the solvent is removed *in vacuo*.

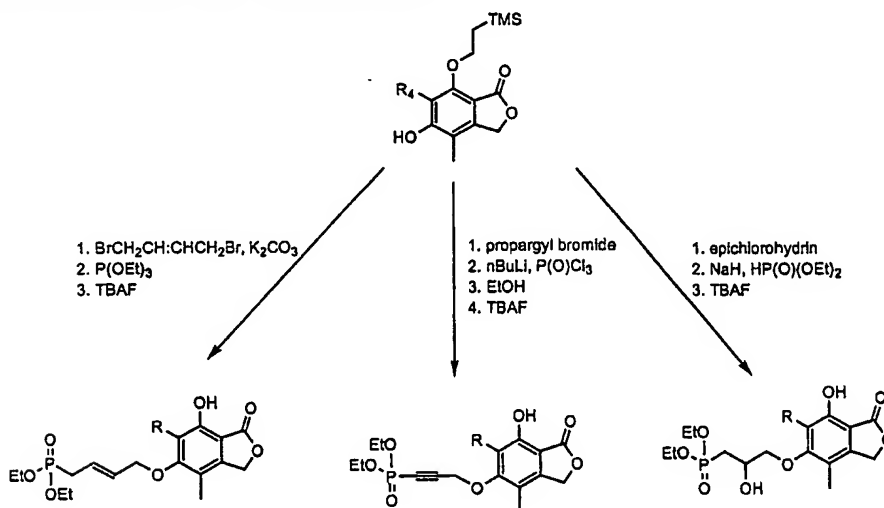
The crude material is dissolved in *N,N* diethylaniline and the reaction mixture is heated at an elevated temperature of *ca.* 180°C. At the end of the
 25 reaction, the mixture is cooled to room temperature and poured into a mixture of aqueous HCl (2N) and ethyl acetate. The organic layer is washed with aqueous HCl (2N) and dried over sodium sulfate. Filtration and removal of the solvents yields the crude product. Further purification is achieved by chromatography.

The product of step 2 is dissolved in a mixture of organic solvents such
 30 as methanol, DCM, and pyridine. The solution is cooled to -78°C and ozone is

bubbled into the solution until a blue color persists. The excess ozone is removed with a nitrogen stream. The reaction mixture is warmed to room temperature and thiourea is added. Stirring at room temperature is continued. The reaction mixture is filtered and partitioned between DCM and water. The aqueous layer is extracted with DCM and the combined organic layers are washed with HCl (1 N), saturated aqueous sodium bicarbonate solution and brine. The solution is dried over sodium sulfate. Filtration and evaporation of the solvents yields the crude aldehyde. Further purification is achieved by chromatography.

The aldehyde is dissolved in an organic solvent such as THF and is reacted with triphenylphosphonium *sec*.propyl bromide and potassium *tert*.butoxide, according to procedures reviewed in *Chem. Rev.*, **1989**, 89, 863-927. At the end of the reaction, the solvent is removed *in vacuo* and the crude material purified by chromatography.

Introduction of linkers to phosphonates

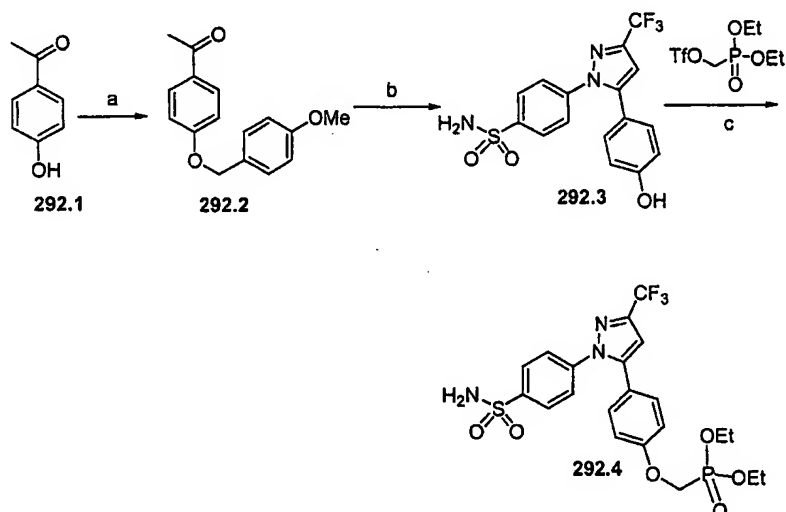


The phenols shown herein may optionally be alkylated with the reagent of choice. Optionally, the phosphonate moiety will be part of such a reagent. Alternatively, it will be introduced in a subsequent step by a variety of means, of which three are illustrated above. For example, an alkyl halide may be heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction

conditions: see Engel, R., "Synthesis of Carbon-phosphorus Bonds," CRC press, 1988). Alternatively, an epoxide may be reacted with the anion of a dialkyl phosphinate. In a further example, the phosphonate reagent may be the electrophile, *e.g.*, an acetylide anion may be condensed with phosphorus
5 oxychloride and the intermediate dichlorophosphonate quenched with ethanol to generate the diethyl ester of the desired phosphonic acid.

Example 292: Preparation of Representative Celecoxib Compounds of the Invention

Specific compounds of the invention can be prepared as illustrated as follows.



Reagents & Conditions: (a) PMBCl, K₂CO₃, acetone, rt; (b) (i) CF₃COOEt, NaH, THF, -20°C-rt; (ii) 4-sulfonamidophenylhydrazine, EtOH, reflux, overnight; (c) Cs₂CO₃, DMF, 0°C-rt.

Synthesis of Compound 292.2.

4-Hydroxyacetophenone (1.6 g, 11.02 mmol) was dissolved in dry acetone (15 mL) under an argon atmosphere, and *p*-methoxybenzyl chloride (1.42 mL, 12.12 mmol) was added, followed by powdered K₂CO₃ (2.28 g, 16.53 mmol) at room temperature. The reaction mixture was stirred overnight and solids were filtered off. The filtrate was concentrated to a syrup, dissolved in 20 mL of CHCl₃ and washed with deionized water (2x 5 mL). The organic layer

was dried over Na₂SO₄, concentrated and purified by silica gel column chromatography (cyclohexane : EtOAc, 2 : 1) to afford pure compound **292.2** as semi-solid (600 mg, 22%). ESI-MS: *m/z* 257 [M+H]⁺.

Synthesis of compound 292.3.

5 **Step 1.** Compound **292.2** (100 mg, 0.39 mmol) was dissolved in dry THF (3 mL) and cooled to -20 °C. NaH (24 mg, 0.98 mmol) was added. The mixture was stirred for 5 minutes and ethyl trifluoroacetate (56 µL, 0.47 mmol) was added at -20 °C. The mixture was allowed to warm to room temperature with stirring for 24 hours. After cooling to 0°C, MeOH (2mL) was added and
10 the mixture was concentrated to a syrup, which was dissolved in 10 mL of CHCl₃ and washed with 1N HCl (5 mL) and deionized water (5 mL). The organic layer was dried over Na₂SO₄ and concentrated to give a light yellow semi-solid compound (130 mg) that was used without further purification.

Step 2. The crude product from Step 1 (130 mg, 0.37 mmol) was
15 dissolved in absolute ethanol (10 mL). 4-Sulfonamidophenylhydrazine hydrochloride (105 mg, 0.56 mmol) was added, and the reaction mixture was heated at reflux overnight, after which TLC (Cyclohexane : EtOAc, 2 : 1) showed complete consumption of starting material. The mixture was cooled, concentrated to a syrup, dissolved in 20 mL of EtOAc, washed with deionized
20 water (2x5 mL), dried over Na₂SO₄ and concentrated to give a yellow syrup. Purification by silica gel column chromatography (cyclohexane : EtOAc, 2 : 1) afforded the compound as light yellow solid (123 mg, 66%). HPLC: 98.6% pure (Sphereclone 5 µL, H₂O : MeCN, 20 min linear from 10-90% MeCN, 1.0 mL/min). ESI-MS: *m/z* 384 [M+H]⁺. ¹H NMR (300 MHz, DMSO-d₆, D₂O
25 exchanged): δ 7.88-7.85 (2H, m, ArH), 7.54-7.50 (2H, m, ArH), 7.13-7.09 (3H, m, ArH), 6.79-6.75 (2H, m, ArH).

Synthesis of compound 292.4.

 Compound **292.3** (70 mg, 0.14 mmol) was dissolved in 3 mL of dry DMF under an argon atmosphere. Diethylphosphonomethyl-*O*-triflate (51 mg,
30 0.17 mmol) and Cs₂CO₃ (69 mg, 0.21 mmol) were added. The reaction mixture was stirred overnight at room temperature. Deionized water (10 mL) was added and the mixture was extracted with ethyl acetate (2x15 mL). The ethyl acetate

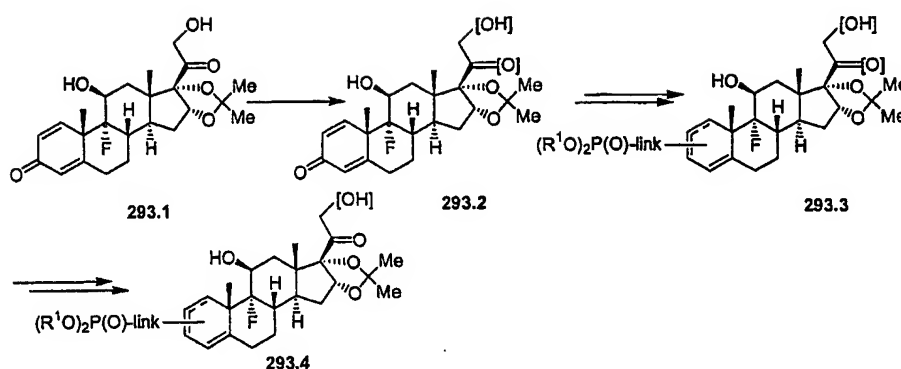
layer was washed with 1N HCl (5 mL) and deionized water (10 mL) and dried over Na₂SO₄. Concentration gave a syrup that on purification by preparative-TLC (1 plate, 20x20 cm, 2000 microns, solvent: CHCl₃ : MeOH, 95 : 5) gave a gummy yellow solid (20 mg, 27% yield). HPLC: 97.8% pure (Sphereclone 5
5 μ L, H₂O : MeCN, 20 min linear from 10-90% MeCN, 1.0 mL/min). ESI-MS: m/z 534 [M+H]⁺. ¹H NMR (300 MHz, CDCl₃): δ 7.91 (2H, d, J = 8.8 Hz, ArH), 7.46 (2H, d, J = 8.8 Hz, ArH), 7.16 (2H, d, J = 8.9 Hz, ArH), 6.96 (2H, d, J = 8.9 Hz, ArH), 6.73 (1H, s, CH), 5.07 (2H, br s, NH), 4.31-4.22 (6H, m, 3xOCH₂), 1.37 (6H, t, J = 7.1 Hz, 2xCH₃). ³¹P NMR (CDCl₃, H₃PO₄ as external
10 reference): δ 19.14

Example 293: Preparation of Representative Triamcinolone Acetonide Derivatives

15 The syntheses of the phosphonate compounds of this invention, and of the intermediate compounds involved in their synthesis, is described below.

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to
20 protect certain reactive substituents from unwanted reactions by protection before the described reaction, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis (Second Edition, Wiley, 1991).
25 The protection and deprotection of steroidal ketones and alcohols is described in J. Fried and J. A. Edwards, Organic Reactions in Steroid Chemistry, Vol. 1 375ff (van Nostrand Reinhold, 1972). Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], *etc.*



For example, a protection-deprotection sequence is depicted above in which the 20-ketone group and/or the 21-hydroxyl group of Triamcinolone acetonide **293.1** are protected to afford the derivative **293.2**. The ketone is
 5 protected, for example, by conversion to the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, 77:1904 (1955). Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in *J. Chem. Soc. Chem. Comm.* 1351 (1987).

10 Alternatively, the 20-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone **293.1** with N,N-dimethylhydrazine in ethanol-acetic acid, as described in *Org. Syn.* 50:102 (1970). The group is removed by treatment with sodium acetate and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.* 101:5841 (1979).
 15

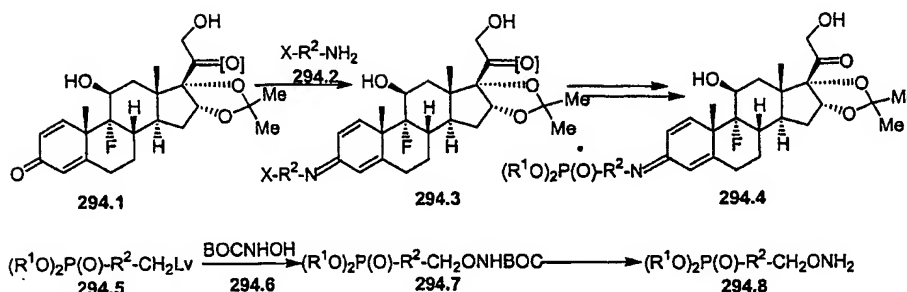
Alternatively, the 20-ketone is protected as the diethylamine adduct. In this procedure, the substrate **293.1** is reacted with titanium tetrakis(diethylamide), as described in *J. Chem. Soc. Chem. Comm.* 406 (1983), to afford the adduct. The ketone is deprotected by reaction with water in an
 20 aqueous organic solvent.

The 21-hydroxyl group is protected, for example, by conversion to the acetate ester by reaction with one molar equivalent of acetyl chloride in dichloromethane/pyridine. The 21-acetoxy group is removed by reaction with one molar equivalent of lithium hydroxide in aqueous dimethoxyethane.

Alternatively, the 21-hydroxyl group is protected by conversion to the tert. butyl dimethylsilyl ether, by reaction in dimethylformamide solution with one molar equivalent of tert. butylchlorodimethylsilane and imidazole, as described in *J. Am. Chem. Soc.*, 94: 6190, 1972. The silyl ether is removed by
5 reaction with tetrabutylammonium fluoride in tetrahydrofuran solution, as described in *J. Am. Chem. Soc.* 94:6190 (1972).

The protected compound **293.2** is then converted into the phosphonate-containing analog **293.3**, using the procedures described below, and the protecting group or groups are then removed, as described above, to give the
10 phosphonate **293.4**.

Example 294: Preparation of Representative Triamcinolone Acetonide Derivatives



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The preparation of phosphonates of compounds of the invention in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is shown above.

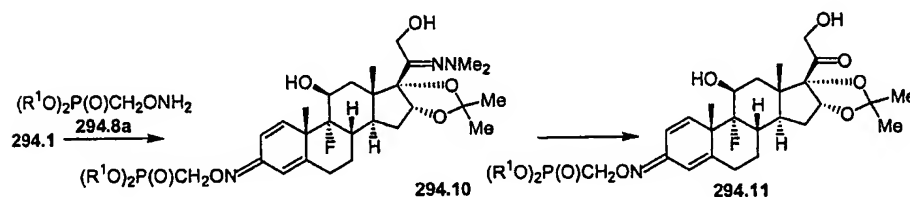
In this procedure, the ketone-protected derivative 294.1 is reacted with an amine or hydroxylamine 294.2, in which R² is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone, *etc.*, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group that is subsequently converted into a phosphonate-containing substituent. For example, X may be dialkylphosphono, bromo, hydroxy, amino, carboxy and the like.

The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime 294.3. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.* 86:133 (1978) and in *J. Mass. Spectrom.* 30:497 (1995). The protecting group is then removed, as described in Example 171, to afford the 20-keto phosphonate product 294.4.

Also illustrated above is the preparation of hydroxylamine ethers incorporating a phosphonate group. In this procedure, a phosphonate 294.5, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is

reacted with BOC-hydroxylamine **294.6** (Aldrich) to produce the ether **294.7**.

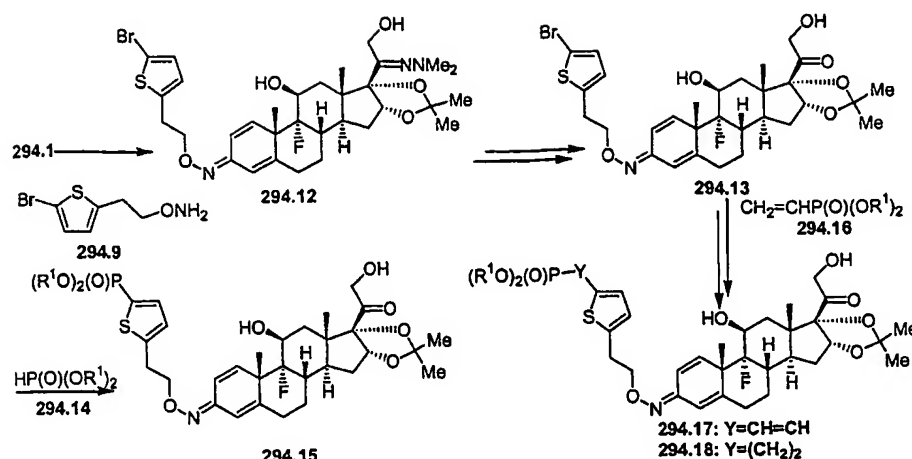
The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether **294.8**. The above procedure is also employed for the preparation of substituted hydroxylamines which are precursors to phosphonates.



The preparation of specific compounds of the invention is shown above.

In particular, the preparation of phosphonates of the invention in which the phosphonate is attached by means of an iminoxy group is shown. In this procedure, the substrate **294.1**, in which the 20-ketone is protected as the dimethyl hydrazone derivative, is reacted with a dialkyl phosphonomethyl hydroxylamine **294.8a**, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tetrahedron Lett.* 27:1477 (1986)) and BOC-hydroxylamine, to afford the oxime **294.10**. Deprotection, as described herein, *e.g.*, in Example 171, then affords the 20-keto phosphonate **294.11**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether **294.8a**, different oxime ethers **294.2**, the corresponding products **294.4** are obtained.

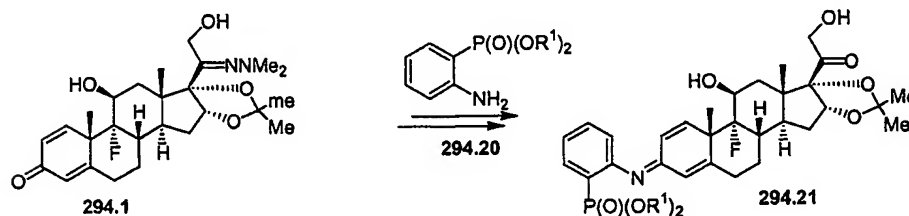


Synthesis of specific compounds of the invention is illustrated above. In particular, the preparation of compounds of the invention in which the phosphonate group is attached by means of a thienylethoxy oxime group is shown. In this procedure, the dienone **294.1**, in which the 20-ketone is protected as the dimethyl hydrazone, is reacted, as described above, with O-(5-bromo-2-thienylethoxy)hydroxylamine **294.9**, prepared as described above from 5-bromo-2-thienylethyl bromide (Syn., 2003, 455), and BOC-protected hydroxylamine **294.6**, to give the oxime **294.12**. The protecting group is then removed to yield the 20-keto product **294.13**. The latter product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **294.14** to afford the phosphonate **294.15**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.* 35:1371 (1992). The reaction is performed at ca. 100° in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Alternatively, the bromo compound **294.13** is coupled with a dialkyl vinyl phosphonate **294.16** (Aldrich) to afford the phosphonate **294.17**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry* 503ff (Plenum, 2001) and in *Acc. Chem. Res.* 12:146 (1979). The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as

tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product **294.17** is reduced, for example by reaction with diimide, to produce the saturated analog **294.18**. The reduction of olefinic bonds is described in R. C. Larock, Comprehensive Organic Transformations 6ff (VCH 1989). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

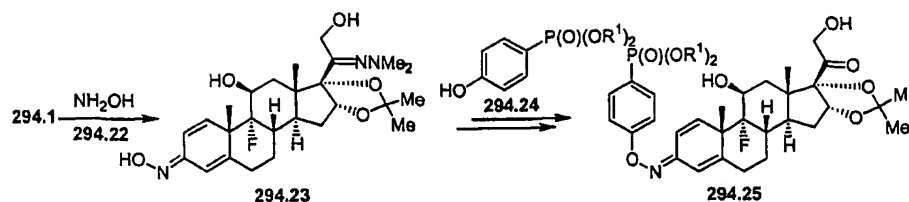
Using the above procedures, but employing, in place of the bromothienylethyl reagent **294.9**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds **294.15**, **294.17** and **294.18** are obtained.



15

The preparation of phosphonates of the invention in which the phosphonate is attached by means of a 2-phenylimino group is illustrated above. In this procedure, the substrate **294.1**, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with a dialkyl 2-aminophenyl phosphonate **294.20** (Syn., 1999, 1368), to give, after deprotection, the imine product **294.21**. The imine forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions.

Using the above procedures, but employing, in place of the 2-aminophenyl phosphonate **294.20** different amino-substituted aryl or heteroaryl phosphonates, products analogous to **294.21** are obtained.

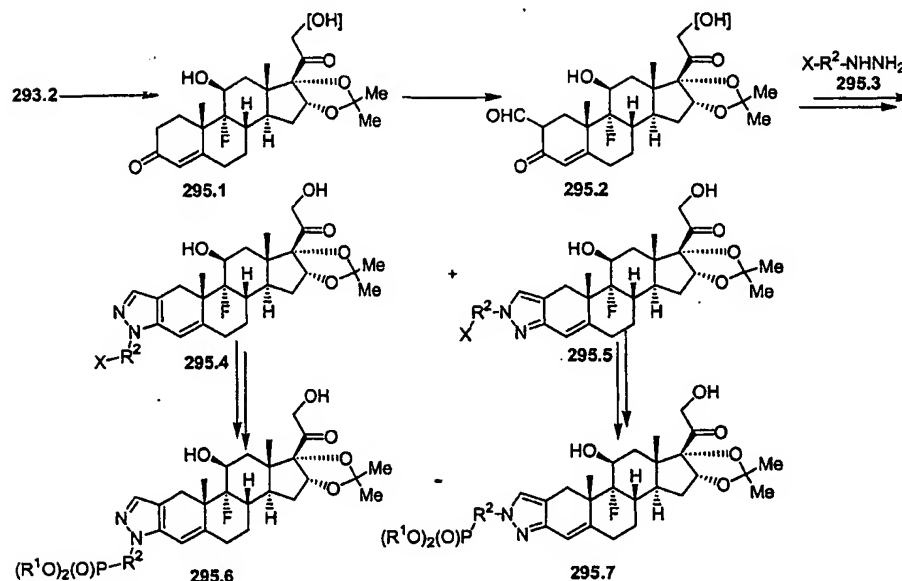


Illustrated above is the preparation of phosphonates of the invention in which the phosphonate is attached by means of an oximino group and an ether linkage. In this procedure, the dienone **294.1**, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with hydroxylamine **294.22** to yield the oxime **294.23**. The reaction of steroidal 1,4-dien-3-ones with hydroxylamines is described in *J. Steroid Bioch.* 7:795 (1976). The reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate.

The product **294.23** is then coupled, in a Mitsunobu reaction, with a dialkyl 4-hydroxyphenyl phosphonate **294.24** (Epsilon), to yield, after deprotection, the ether oxime **294.25**. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in R. C. Larock, *Comprehensive Organic Transformations* 448 (VCH, 1989), in F.A. Carey and R. J. Sundberg, *Advanced Organic Chemistry, Part B* 153-4 (Plenum, 2001), and in *Org. React.* 42:335, (1992). The phenol and the hydroxyl component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.* 42:335-656 (1992).

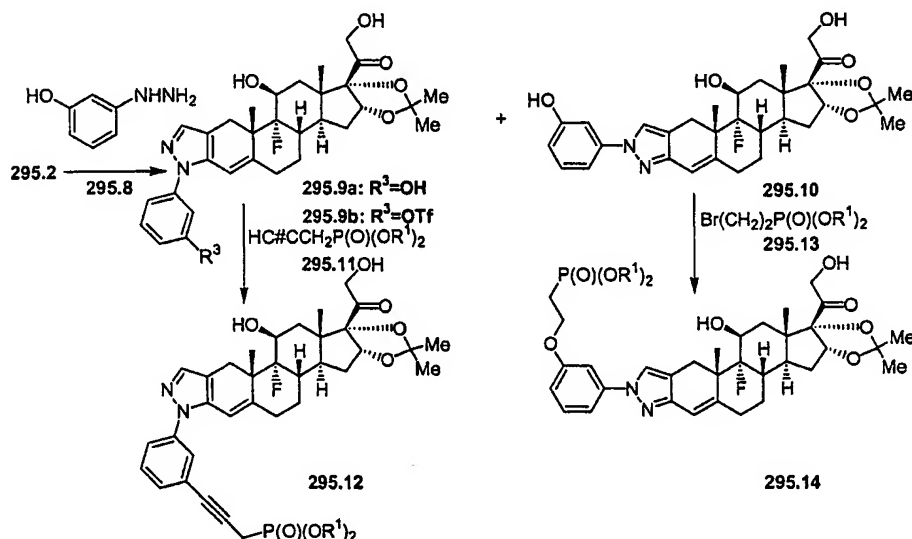
Using the above procedures, but employing, in place of the hydroxyaryl-substituted phosphonate **294.24**, different hydroxyaryl-substituted phosphonates, the products analogous to **294.25** are obtained.

Example 295: Preparation of Representative Triamcinolone Acetonide Derivatives



- 5 Illustrated above is the preparation of phosphonate esters of the invention in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and/or a variable carbon chain. In this procedure, the dienone 293.1, in which the 21-hydroxyl group is protected as described in Example 293, is reduced to afford
- 10 the 1,2-dihydro product 295.1. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.* 44:602 (2001). The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.* 86:1520 (1964), to afford
- 15 the 2-formyl product 295.2. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine 295.3, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X may be dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields, after
- 20 deprotection of the 21-hydroxyl group, the isomeric 2'- and 1'-aryl pyrazoles

295.4 and 295.5. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.* 86:1520 (1964). The pyrazoles 295.4 and 295.5 are then transformed, for example by the procedures described herein, into the phosphonates 295.6 and 295.7.

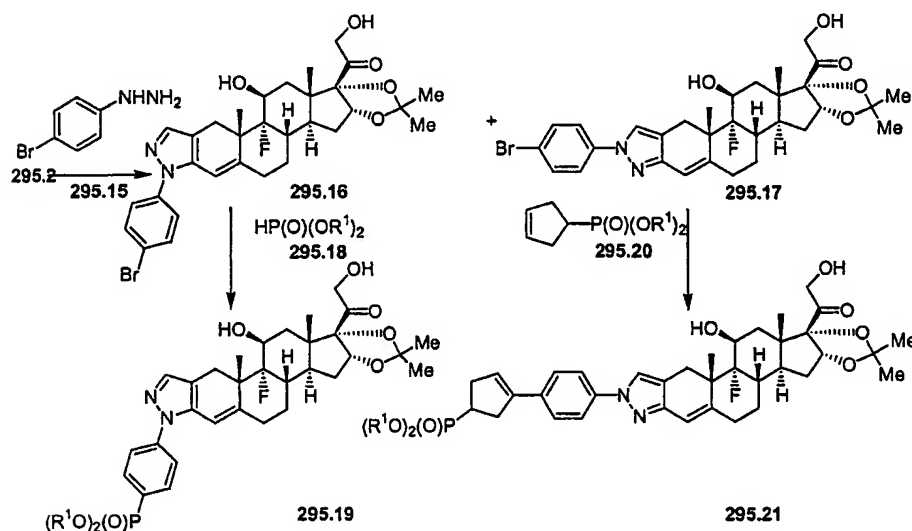


The preparation of specific compounds of the invention in which the phosphonate is attached by means of an ether or an acetylenic linkage is shown above.

In this procedure, the ketoaldehyde 295.2 is reacted, as described above, with 3-hydroxyphenyl hydrazine 295.8 (JP 03011081) to give the pyrazoles 295.9a and 295.10. The 2'-substituted isomer 295.9a is then reacted in dichloromethane solution with one molar equivalent of trifluoromethanesulfonyl chloride and pyridine, to give the triflate 295.9b. The product is then reacted in toluene solution with a dialkyl propynyl phosphonate 295.11 (Syn 1999, 2027), triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium (0), to give the acetylenic product 295.12. The palladium-catalyzed coupling reaction of aryl triflates with terminal acetylenes is described in WO 0230930.

The isomeric pyrazole **295.10** is reacted, in dimethylformamide solution at 70°, with one molar equivalent of a dialkyl 2-bromoethyl phosphonate **295.13** (Aldrich) and potassium carbonate to yield the ether phosphonate **295.14**.

Using the above procedures, but employing different hydroxy-substituted hydrazines, and/or different acetylenic or bromo-substituted phosphonates, products analogous to **295.12** and **295.14** are obtained.

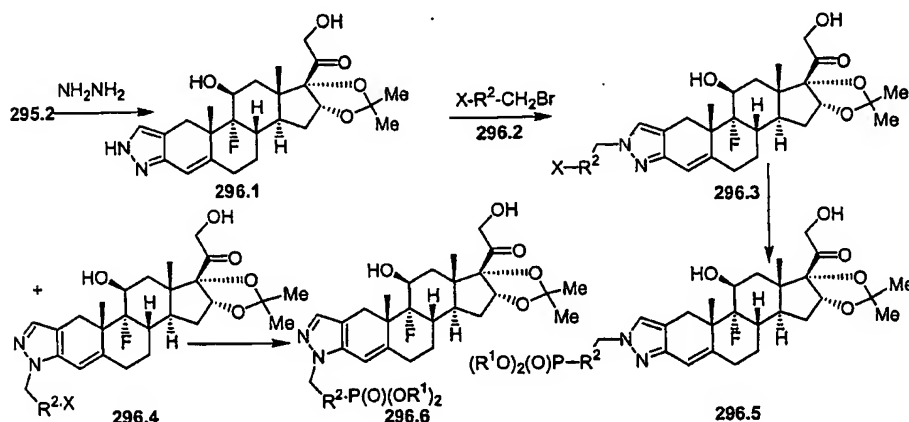


The preparation of phosphonates of the invention in which the phosphonate group is attached by means of a phenyl group or a phenylcyclopentenyl linkage is shown above. In this procedure, the ketoaldehyde **295.2** is reacted, as described above, with 4-bromophenyl hydrazine **295.15** (*J. Organomet. Chem.*, 62:581(1999)) to produce the pyrazoles **295.16** and **295.17**. The 2'-substituted isomer **295.16** is then coupled, as described above, with a dialkyl phosphite **295.18** to give the phosphonate **295.19**. Alternatively, the 1'-substituted pyrazole **295.22** is coupled in a Heck reaction, as described above, with a dialkyl cyclopentenyl phosphonate **295.20** (*Syn. Comm.*, 28:83(1998)) to prepare the cyclopentenyl phosphonate **295.21**. Using the above procedures, but employing, in place of the 4-bromophenyl hydrazine **295.15**, different bromo-substituted hydrazines, and/or

different dialkyl alkenyl-substituted phosphonates, the products analogous to the compounds **295.19** and **295.21** are obtained.

Example 296: Preparation of Representative Triamcinolone Acetonide

5 Derivatives



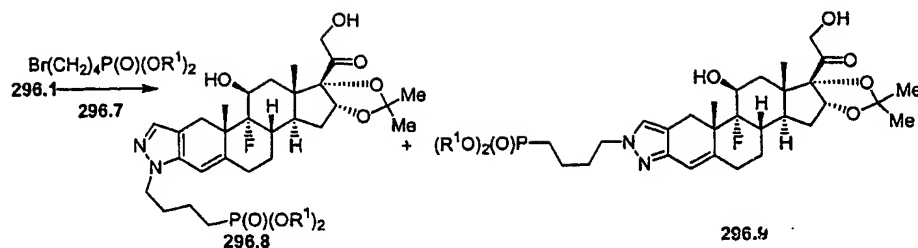
The preparation of phosphonate esters of the invention in which the phosphonate group is attached by means of a variable carbon linkage is

10 illustrated above.

In this procedure, the ketoaldehyde **295.2** is reacted with hydrazine to afford the pyrazole derivative **296.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, 86:1520 (1964). The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound **296.2**, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products **296.3** and **296.4**. The alkylation of substituted pyrazoles is described, for example, in T. L. Gilchrist, *Heterocyclic Chemistry* 309 (Longman, 1992). The reaction is performed between equimolar amounts of the

15 substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products **296.3** and **296.4** are, except in cases where X is dialkylphosphono, converted into the phosphonates **296.5** and **296.6**, using the procedures described herein.

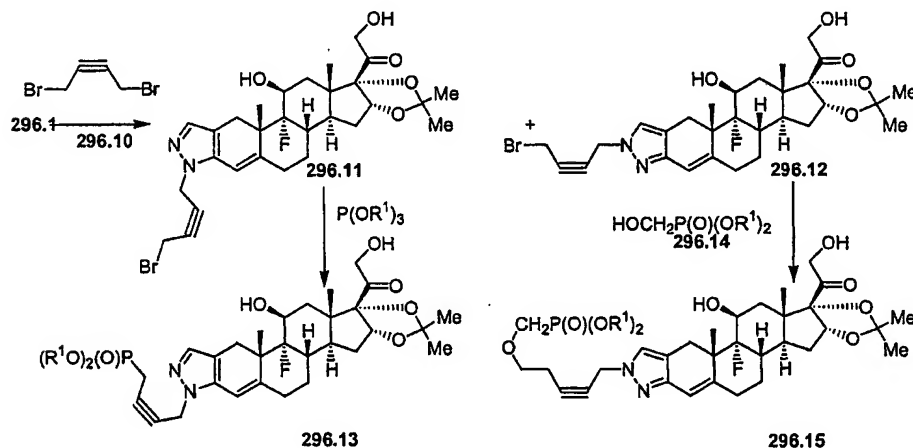
20



Specific compounds of the invention are shown above. The pyrazole

- 5 296.1 is reacted in dimethylformamide solution at 70° with one molar equivalent of a dialkyl 4-bromobutyl phosphonate 296.7 (Synthelec) and cesium carbonate, to give the pyrazoles 296.8 and 296.9.

Using the above procedures, but employing different bromo-substituted phosphonates, the products analogous to 296.8 and 296.9 are obtained.



10

- Specific compounds of the invention are shown above. The pyrazole 296.1 is reacted in tetrahydrofuran solution with 1,4-dibromobut-2-yne 296.10 and potassium hexamethyl disilazide, to give the alkylation products 296.11 and 296.12. The 2'-substituted isomer 296.11 is then reacted, in a Arbuzov reaction, with a trialkyl phosphite to yield the phosphonate 296.13. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, 115 (1992). In this procedure, in which a bromo substituent is converted into the corresponding phosphonate,
- 15

the substrate is heated at from about 60° to about 160° with a five to fifty-fold molar excess of a trialkyl phosphite, to effect the transformation.

The 2'-substituted pyrazole 296.14 is reacted at 70° in dimethylformamide solution with one molar equivalent of a dialkyl hydroxymethyl phosphonate 296.14 (Aldrich) and cesium carbonate, to give the ether phosphonate 296.15.

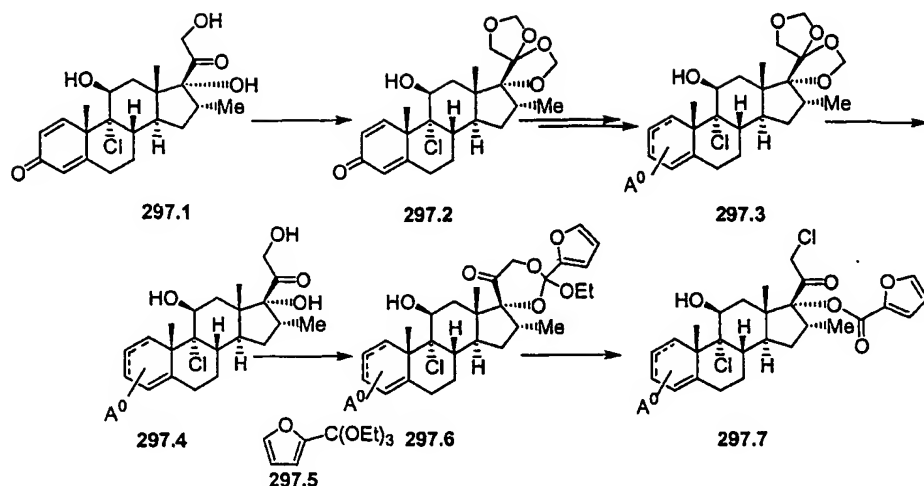
Using the above procedures, but employing different dibromides, and/or different hydroxyl-substituted phosphonates, the products analogous to 296.13 and 296.15 are obtained.

Example 297: Preparation of Representative Mometasone Furoate Derivatives

Preparation of representative compounds of the invention is described hereinbelow.

Protection of reactive substituents

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the described sequence is reacted, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. The protection and deprotection of steroidal ketones and alcohols is described in Organic Reactions in Steroid Chemistry, Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], etc.



For example, depicted above is a protection-deprotection sequence in which the steroid side-chain is protected as a bis-methylenedioxy (BMD) moiety. In this sequence, 9 α -chloro-16 α -methyl-11 β ,17 α ,21-trihydroxypregn-1,4-dien-3,21-dione **297.1** (U.S. Patent No. 4,472,393) is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in “Protective Groups in Organic Synthesis,” by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to yield the BMD derivative **297.2**.

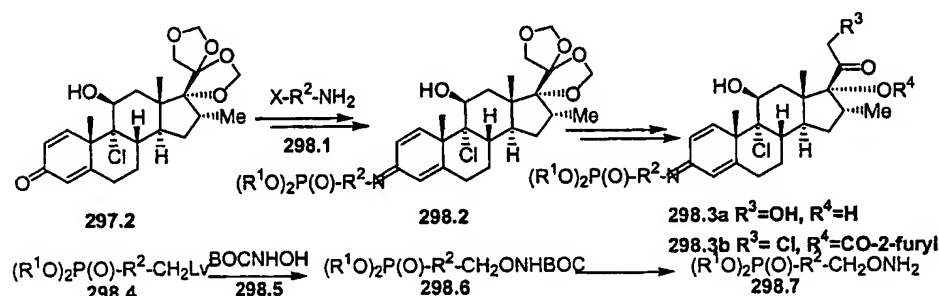
The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester **297.3**. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in “Protective Groups in Organic Synthesis,” by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 223, to afford the triol **297.4**. The latter compound is then converted into the 17,21-cyclic orthoester **297.6** using the procedure described in *Chem. Pharm. Bull.*, 34:1613(1986). The substrate is reacted in dimethylformamide at 70°C with two molar equivalents of triethyl ortho-2-furoate **297.5** (*Zh. Org. Khim.*, 50:1348(1980)) and a catalytic amount of p-toluenesulfonic acid. The product is then reacted with an excess of trimethylsilyl chloride in dimethylformamide at ambient temperature to produce the 21-chloro 17-(2-furoate) product **297.7**.

Alternatively, the substrate **297.4** is converted into the product **297.7** by means of the method described in *J. Med. Chem.*, 1987, 30:1581(1987). In this

procedure, the 21-hydroxy group is activated by conversion to the 21-mesylate, by reaction with mesyl chloride in pyridine; the mesylate group is then displaced to yield the 21-chloro intermediate, by reaction with lithium chloride in dimethylformamide, and the 17-hydroxyl group is esterified to give the 21-chloro-17-(2-furoate) derivative **297.7**. The selective acylation of the 17 α -hydroxyl group in the presence of an 11 β hydroxyl group is described in *J. Med. Chem.*, 30:1581(1987).

Example 298: Preparation of Representative Mometasone Furoate

10 Derivatives

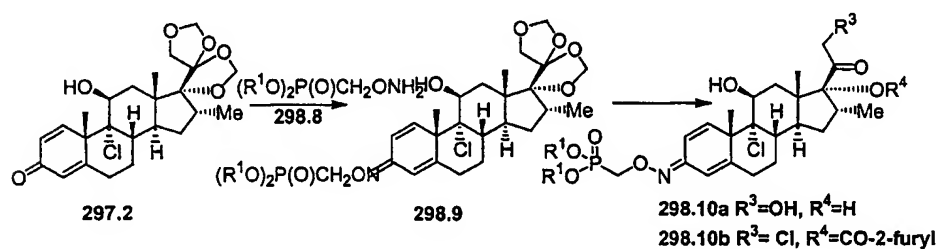


The preparation of phosphonates of the invention in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above.

In this procedure, the BMD-protected derivative **297.2** is reacted with an amine or hydroxylamine **298.1**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone, *etc.*, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group that is subsequently converted into a phosphonate-containing substituent. For example, X may be dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*,

86:133(1978). and in *J. Mass. Spectrom.*, 30:497(1995). The BMD-protected side-chain compound **298.2** is then converted into the triol **298.3a**, and then to the 21-chloro 17-(2-furoate) product **298.3b**, as described herein.

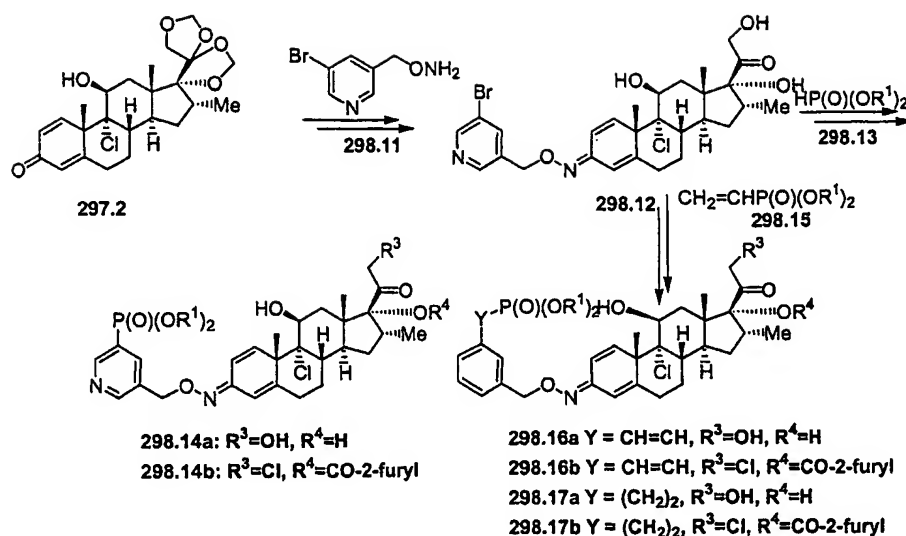
Also illustrated above is the preparation of hydroxylamine ethers
 5 incorporating a phosphonate group. In this procedure, a phosphonate **298.4**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine **298.5** (Aldrich) to produce the ether **298.6**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base
 10 such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether **298.7**.



15

The synthesis of specific compounds of the invention is shown above. The preparation of phosphonates of the invention in which the phosphonate is attached by means of an iminoxy group is illustrated. In this procedure, the substrate **297.2** is reacted with a dialkyl phosphonomethyl hydroxylamine **298.8**,
 20 prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tet. Lett.*, 27:1477(1986)) and BOC-hydroxylamine, to afford the oxime **298.9**. Deprotection then affords the triol **298.10a** from which the 21-chloro 17-(2-furoate) compound **298.10b** is prepared, using the procedures described in Example 297. The oxime forming reaction is performed at ambient
 25 temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether **298.8**, different oxime ethers **298.1**, the corresponding products **298.3b** are obtained.



- 5 The synthesis of specific compounds of the invention is shown above.
- The preparation of compounds of the invention in which the phosphonate group is attached by means of a pyridylmethoxy oxime group is illustrated above. In this procedure, the dienone **297.2** is reacted, as described above, with O-(5-bromo-3-pyridylmethoxy)hydroxylamine **298.11**, prepared as described above
- 10 from 5-bromo-3-bromomethylpyridine (EP 511865) and BOC-protected hydroxylamine **298.5**, to give, after deprotection of the side-chain, the oxime **298.12**. The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **298.13** to afford the phosphonate **298.14a**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, 35: 1371(1992). The reaction
- 15 is performed at ca. 100°C in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0). The 21-hydroxy compound **298.14a** is then converted, as described in Example 297, into the 21-chloro 17-(2-furoate) derivative **298.14b**.
- 20

Alternatively, the bromo compound **298.12** is coupled with a dialkyl vinyl phosphonate **298.15** (Aldrich) to afford the phosphonate **298.16a**. The

coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, "Advanced Organic Chemistry," 503ff (Plenum, 2001) and in *Acc. Chem. Res.*, 12:146 (1979). The aryl bromide and the olefin are coupled in a polar solvent such as

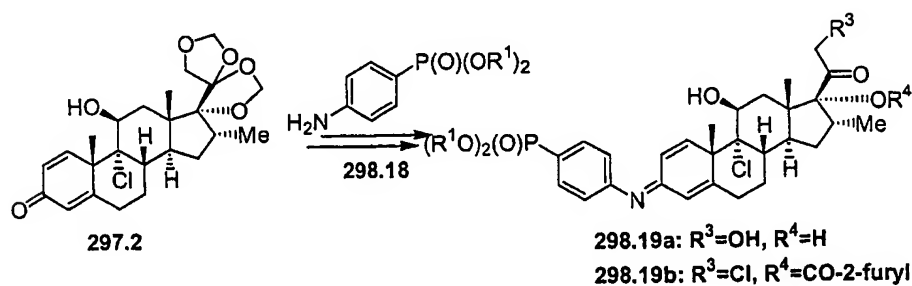
5 dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the double bond present in the product **298.16a** is reduced, for example by reaction with diimide, to produce the

10 saturated analog **298.17a**. The reduction of olefinic bonds is described in R. C. Larock, "Comprehensive Organic Transformations," 6ff (VCH, 1989). The transformation is effected by means of catalytic hydrogenation, for example, using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane. The products **298.16a** and **298.17a** are then

15 converted into the 21-chloro 17-(2-furoate) analogs **298.16b** and **298.17b**.

Using the above procedures, but employing, in place of the bromopyridylmethoxy reagent **298.11**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds **298.14b**, **298.16b** and

20 **298.17b** are obtained.

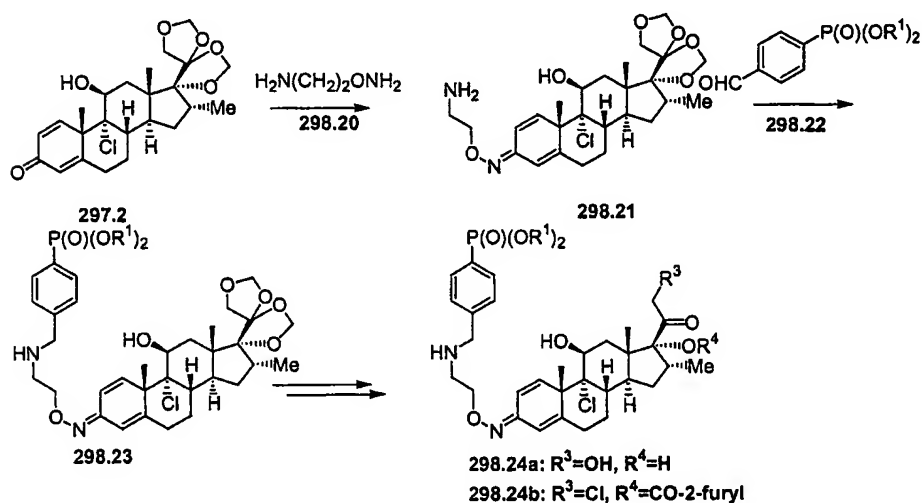


The preparation of specific compounds of the invention is depicted

25 above. The preparation of phosphonates of the invention in which the phosphonate is attached by means of an imino group. In this procedure, the substrate **297.2** is reacted with a dialkyl 4-aminophenyl phosphonate **298.18**

(Epsilon) to give, after deprotection, the imine product **298.19a**. The imine forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions. The product is then converted into the 21-chloro 17-(2-furoate) compound **298.19b**.

Using the above procedures, but employing, in place of the 4-aminophenyl phosphonate **298.18** different amino-substituted aryl or heteroaryl phosphonates, products analogous to **298.19b** are obtained.



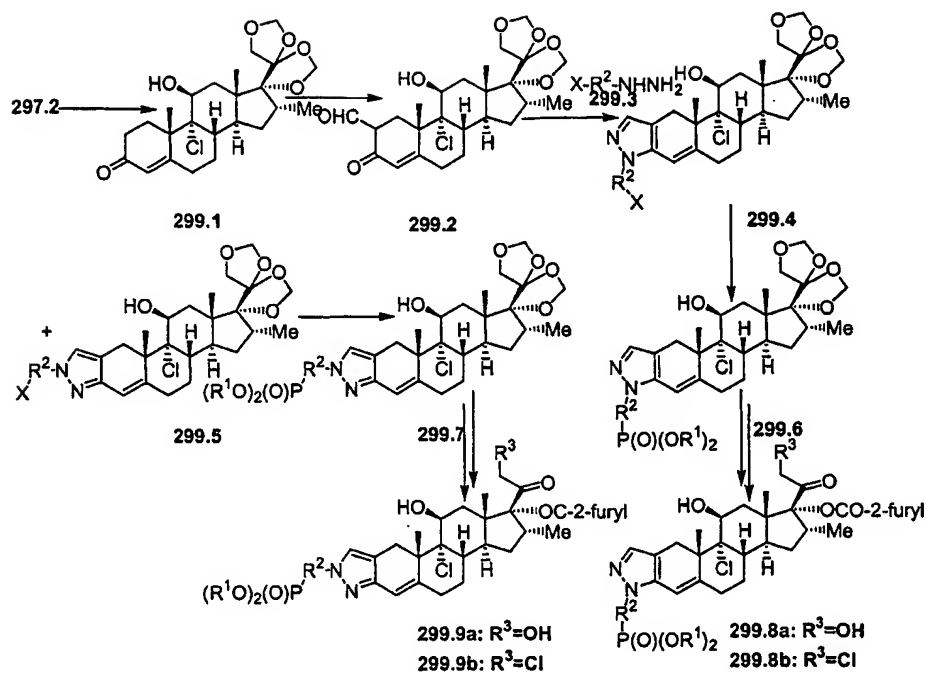
The preparation of specific compounds of the invention is shown above. Phosphonates of the invention in which the phosphonate is attached by means of an oximino group and an amine linkage are illustrated. In this procedure, the dienone **297.2** is reacted with O-(2-aminoethyl)hydroxylamine **298.20** (*Pol. J. Chem.*, 55:1163(1981)) to yield the oxime **298.21**. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.*, 7:795(1976); the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product is then reacted, in a reductive amination procedure, with a dialkyl 4-formylphenyl phosphonate **298.22** (Epsilon) and sodium triacetoxyborohydride, to yield the amine oxime

298.23. The preparation of amines by means of reductive amination procedures is described, for example, in R. C. Larock, "Comprehensive Organic Transformations," 421 (VCH), and in F.A. Carey and R. J. Sundberg, "Advanced Organic Chemistry," Part B, 269 (Plenum, 2001). In this procedure,
5 the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in *J. Org. Chem.*, 55:2552 (1990).

10 The amine product 298.23 is then converted, as described in Example 297, into the 21-chloro 17-(2-furoate) product 298.24b.

Using the above procedures, but employing, in place of the hydroxylamine 298.22, different amino-substituted hydroxylamines, and/or different formyl-substituted phosphonates, the products analogous to 298.24b
15 are obtained.

Example 299: Preparation of Representative Mometasone Furoate Derivatives

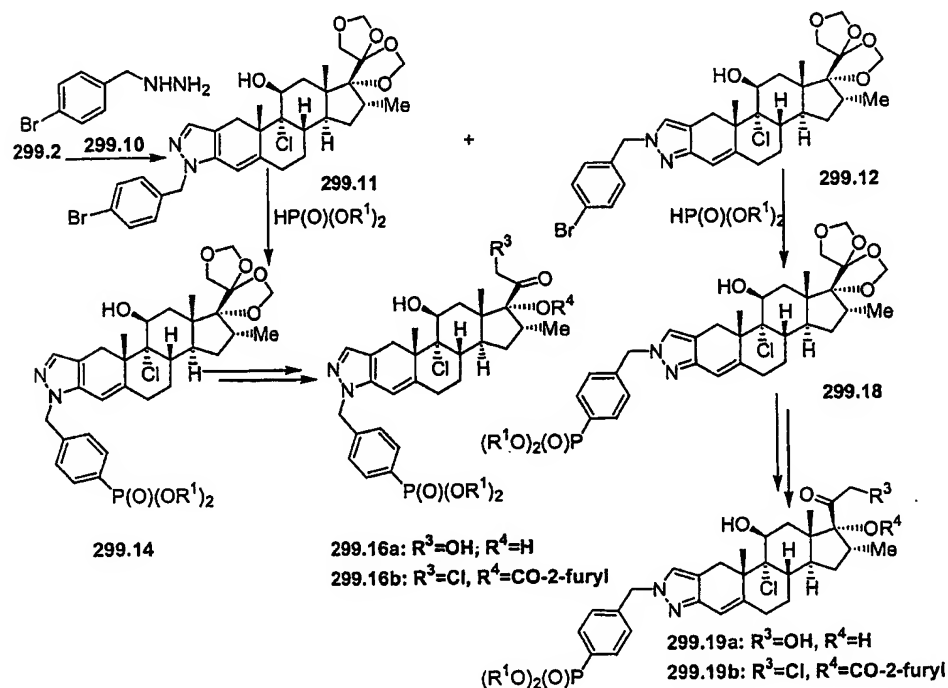


The preparation of phosphonate esters of the invention in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and/or a variable carbon chain is illustrated above.

In this procedure, the BMD-protected dienone **297.2** is reduced to afford the 1,2-dihydro product **299.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, 44:602(2001). The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, 86:1520(1964), to afford the 2-formyl product **299.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine **299.3**, in which the substituent X is either a phosphonate group or a group that is subsequently transformed into a phosphonate-containing substituent. For example, X may be dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles **299.4** and **299.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such

as acetic acid, as described in *J. Am. Chem. Soc.*, 86:1520(1964). The pyrazoles **299.4** and **299.5** are then transformed, for example, by the procedures described herein, *via* the BMD-protected intermediates **299.6** and **299.7**, into the 21-chloro 17-(2-furoate) phosphonates **299.8b** and **299.9b**.

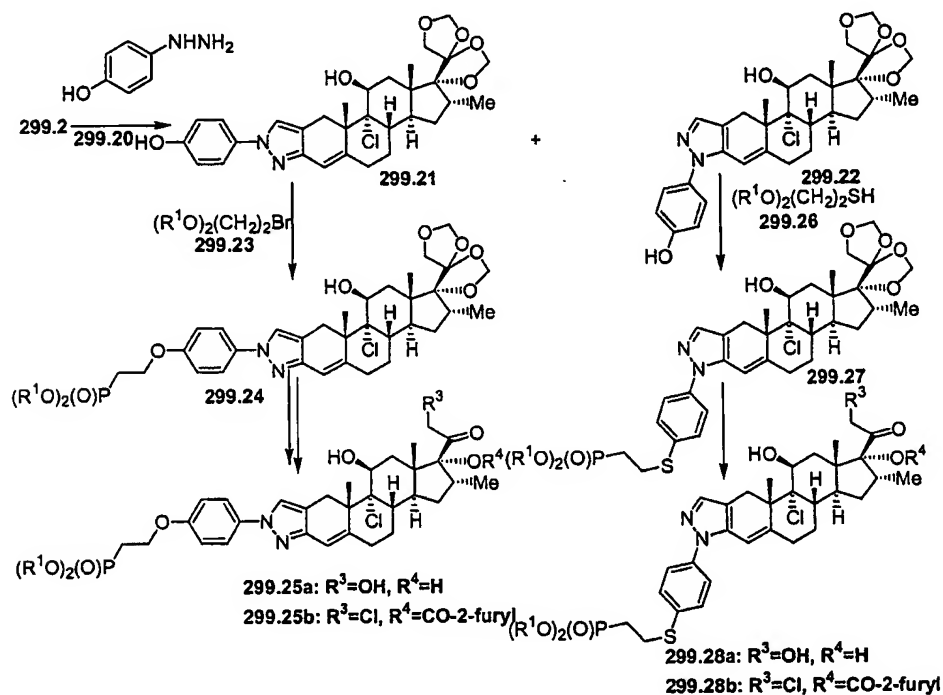
5



The preparation of specific compounds of the invention is depicted above. Phosphonates of the invention in which the phosphonate is attached by means of a benzyl linkage are shown above. In this procedure, the ketoaldehyde **299.2** is reacted, as described above, with 4-bromobenzyl hydrazine **299.10** (*Ann.*, 717:104(1968)) to give the pyrazoles **299.11** and **299.12**. The 2'-substituted isomer **299.11** is then coupled, as described in Example 298, with a dialkyl phosphite, to yield the phosphonate **299.14**. The BMD protecting group is then removed and the product is converted into the 21-chloro 17-(2-furoate) product **299.16b**.

The isomeric pyrazole **299.12** is subjected to the same series of reactions to afford the isomeric product **299.19b**.

Using the above procedures, but employing different bromo-substituted hydrazines, the products analogous to **299.16b** and **299.19b** are obtained.



5

The preparation of specific compounds of the invention is shown above. Phosphonates of the invention in which the phosphonate group is attached by means of a phenyl group and an ether or thioether linkage. In this procedure, the ketoaldehyde **299.2** is reacted, as described above, with 4-hydroxyphenyl hydrazine **299.20** (EP 437105) to produce the pyrazoles **299.21** and **299.22**. The 1'-substituted isomer **299.21** is reacted in dimethylformamide at 70°C, with a dialkyl 2-bromoethyl phosphonate **299.23** (Aldrich) and potassium carbonate, to give the ether phosphonate **299.24**. The product is then deprotected to afford the triol **299.25a** which is converted into the 21-chloro 17-(2-furoate) compound **299.25b**.

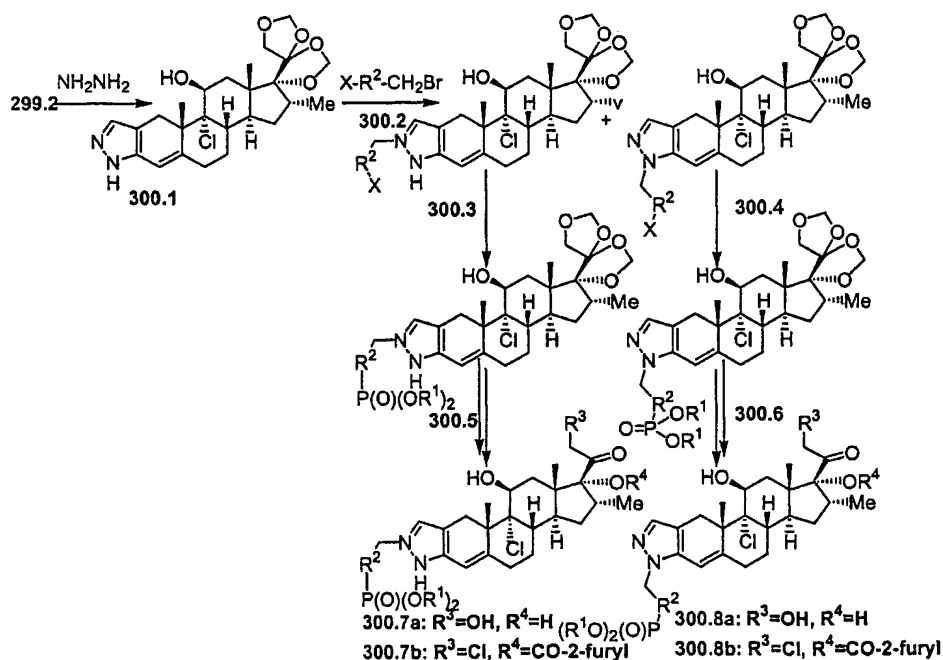
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Alternatively, the 2'-substituted pyrazole **299.22** is coupled, in a Mitsunobu reaction, with a dialkyl 2-mercaptoethyl phosphonate **299.26** (*Zh. Obschei. Khim.*, 43:2364(1973)) to prepare the thioether phosphonate **299.27**, which is deprotected, and the product is converted into the 21-chloro 17-(2-

furoate) analog **299.28b**. The preparation of aromatic ethers and thioethers by means of the Mitsunobu reaction is described, for example, in R. C. Larock, "Comprehensive Organic Transformations," 448 (VCH, 1989), and in F.A. Carey and R. J. Sundberg, "Advanced Organic Chemistry," Part B, 153-4 (Plenum, 2001) and in *Org. React.*, 42:335 (1992). The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, 42:335-656 (1992).

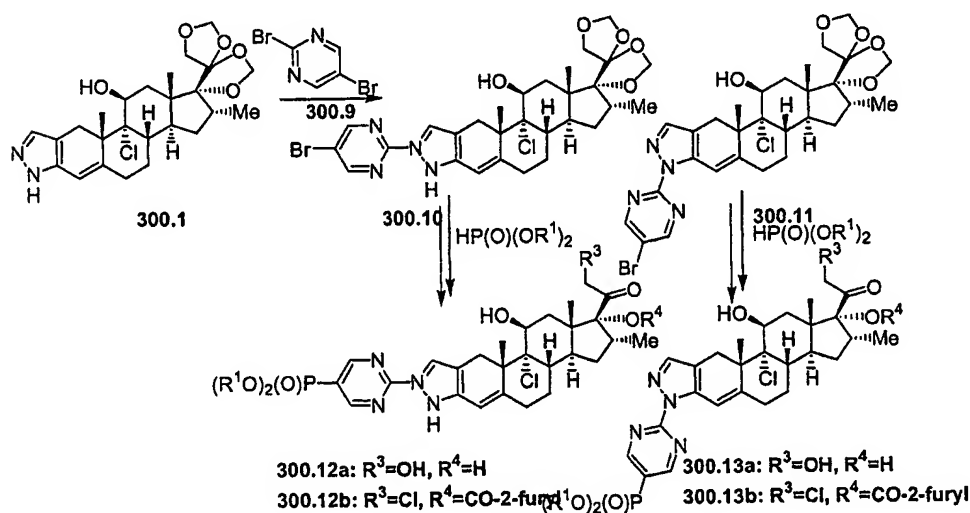
Using the above procedures, but employing, in place of the 4-hydroxyphenyl hydrazine **299.20**, different hydroxy-substituted hydrazines, and/or different dialkyl bromo- or mercapto-substituted phosphonates, the products analogous to the compounds **299.25b** and **299.28b** are obtained.

Example 300: Preparation of Representative Mometasone Furoate Derivatives



The preparation of the phosphonate esters of the invention is shown above.

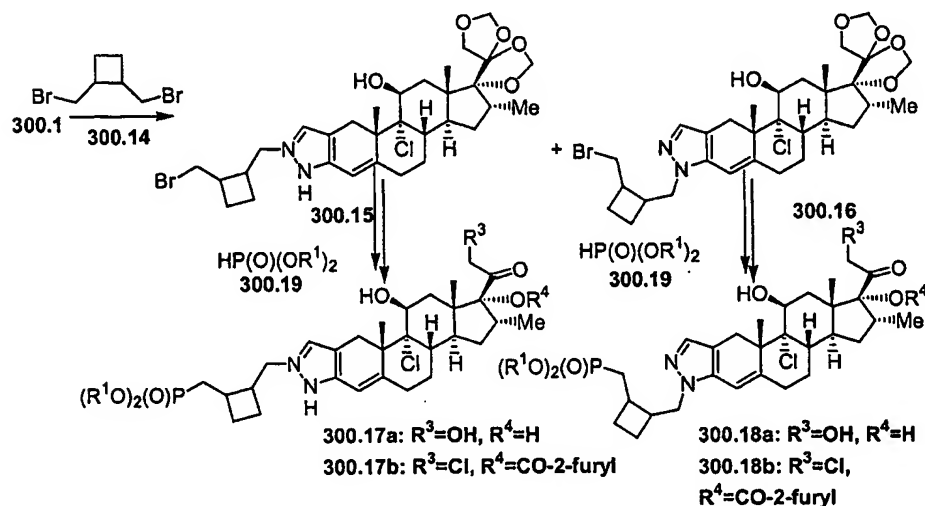
In this procedure, the ketoaldehyde **299.2** is reacted with hydrazine, to afford the pyrazole derivative **300.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, 86:1520 (1964). The
 5 reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound **300.2**, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products **300.3** and **300.4**. The alkylation of substituted pyrazoles is
 10 described, for example, in T. L. Gilchrist, "Heterocyclic Chemistry," 309 (Longman, 1992). The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products **300.3** and **300.4**, except in cases
 15 where X is dialkylphosphono, are converted into the phosphonates **300.5** and **300.6**, using the procedures described herein, and deprotection/chlorination/acylation then affords the 21-chloro 17-(2-furoate) compounds **300.7b** and **300.8b**.



The preparation of specific compounds of the invention is shown above. The pyrazole **300.1** is reacted with 2,5-dibromopyrimidine **300.9** (*Chem. Lett.*,

583 (1992)) to give the pyrazoles **300.10** and **300.11**. The products are then coupled, as described above, with a dialkyl phosphite, to afford after side-chain deprotection and modification, as described above, the 21-chloro 17-(2-furoates) **300.12b** and **300.13b**.

5



Specific compounds of the invention are prepared as shown above. The pyrazole **300.1** is reacted in tetrahydrofuran solution, with 1,2-bis(bromomethyl)cyclobutane **300.14** (*J. Org. Chem.*, 46:3530(1981)) and potassium hexamethyl disilazide, to give the alkylation products **300.14** and **300.15**. The 1'-substituted isomer **300.15** is then reacted, in an Arbuzov reaction, with a trialkyl phosphite to yield, after deprotection and side-chain modification, the 21-chloro 17-(2-furoate) **300.17b**. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, 115 (1992). In this procedure, in which a bromo substituent is converted into the corresponding phosphonate, the substrate is heated at from about 60°C to about 160°C with a five to fifty-fold molar excess of a trialkyl phosphite, to effect the transformation.

The 2'-substituted pyrazole **300.16** is subjected to the same series of reaction to give the amine phosphonate **300.18b**.

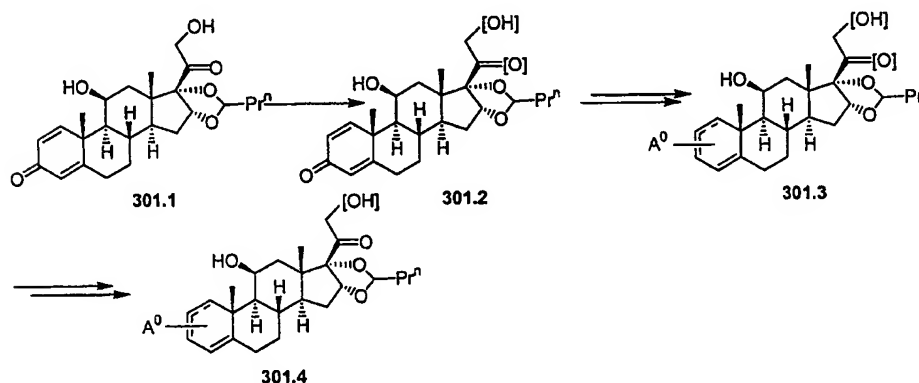
Using the above procedures, but employing different dibromides, the products analogous to **300.17b** and **300.18b** are obtained.

Example 301: Preparation of Representative Budesonide Derivatives

Representative compounds of the invention may be prepared as described herein.

Depending on the reaction conditions employed, it may be necessary to
 5 protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition
 10 1990. The protection and deprotection of steroidal ketones and alcohols is described in "Organic Reactions in Steroid Chemistry," Vol. 1, J. Fried and J. A. Edwards, van Nostrand Reinhold, 1972, p. 375ff. Reactive substituents that may be protected are shown in the accompanying schemes as, for example, [OH],
 [O], *etc.*

15



For example, depicted above is a protection-deprotection sequence in which the 20-ketone group and/or the 21-hydroxyl group of Budesonide 301.1
 20 are protected to afford the derivative 301.2. The ketone is protected, for example, by conversion to the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, 77:1904 (1955). Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in *J. Chem.*
 25 *Soc., Chem. Comm.*, 1351 (1987).

Alternatively, the 20-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone **301.1** with N,N-dimethylhydrazine in ethanol-acetic acid, as described in Org. Syn., 50:102 (1970). The group is removed by treatment with sodium
5 acetate and acetic acid in aqueous tetrahydrofuran, as described in J. Am. Chem. Soc., 101:5841 (1979).

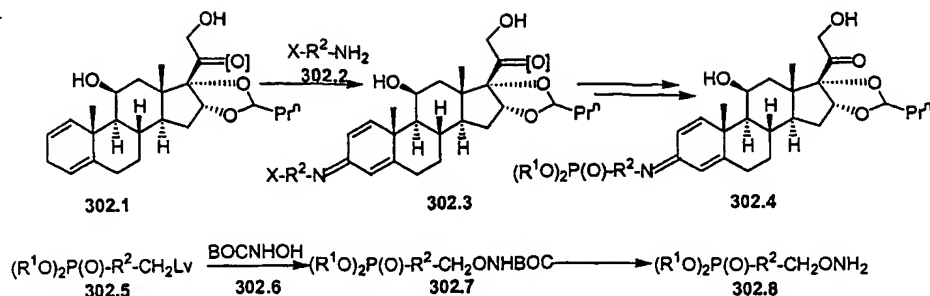
Alternatively, the 20-ketone is protected as the diethylamine adduct. In this procedure, the substrate **301.1** is reacted with titanium
tetrakis(diethylamide), as described in J. Chem. Soc., Chem. Comm., 406
10 (1983), to afford the adduct. The ketone is deprotected by reaction with water in an aqueous organic solvent.

The 21-hydroxyl group is protected, for example, by conversion to the acetate ester, by reaction with one molar equivalent of acetyl chloride in dichloromethane/pyridine. The 21-acetoxy group is removed by reaction with
15 one molar equivalent of lithium hydroxide in aqueous dimethoxyethane.

Alternatively, the 21-hydroxyl group is protected by conversion to the tert. butyl dimethylsilyl ether, by reaction in dimethylformamide solution with one molar equivalent of tert. butylchlorodimethylsilane and imidazole, as described in J. Am. Chem. Soc., 94:6190 (1972). The silyl ether is removed by
20 reaction with tetrabutylammonium fluoride in tetrahydrofuran solution, as described in J. Am. Chem. Soc., 94:6190 (1972).

The protected compound **301.2** is then converted into the phosphonate-containing analog **301.3**, using the procedures described below, and the protecting group or groups are then removed, as described above, to give the
25 phosphonate **301.4**.

Example 302: Preparation of Representative Budesonide Derivatives

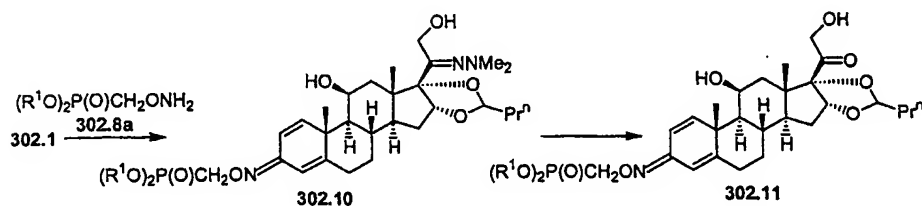


Depicted above is the preparation of compounds of the invention in which the phosphonate is attached by means of an imino or iminox group and a variable carbon chain. In this procedure, the ketone-protected derivative **302.1** is reacted with an amine or hydroxylamine **302.2**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone, *etc.*, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group that is subsequently converted into a phosphonate-containing substituent.

For example, X may be dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime **302.3**. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **86**:133 (1978) and in *J. Mass. Spectrom.*, **30**: 497 (1995). The protecting group is then removed, as described in Example 301, to afford the 20-keto phosphonate product **302.4**.

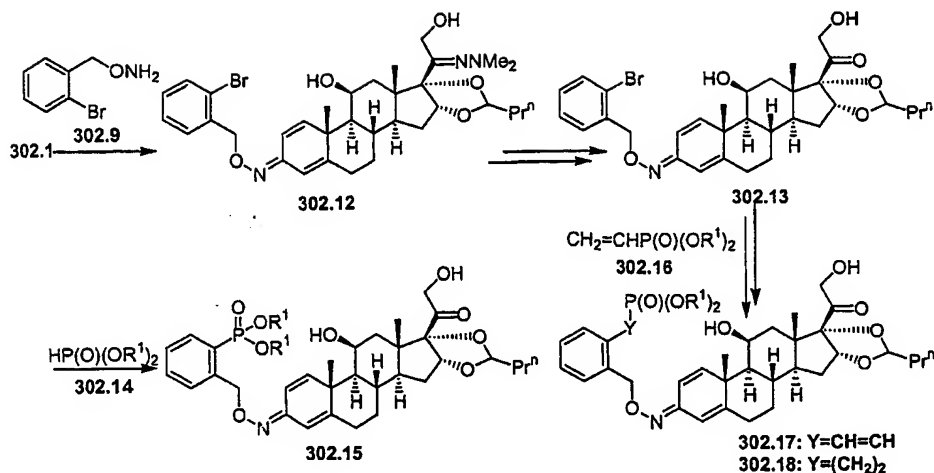
Also illustrated above is the preparation of hydroxylamine ethers incorporating a phosphonate group. In this procedure, a phosphonate **302.5**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine **302.6** (Aldrich) to produce the ether **302.7**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example, by treatment with trifluoroacetic acid, then gives the hydroxylamine

ether **302.8**. The above procedure is also employed for the preparation of substituted hydroxylamines which are precursors to phosphonates.



5 The synthesis of specific compounds of the invention is shown above. The preparation of compounds of the invention in which the phosphonate is attached by means of an iminoxy group is illustrated. In this procedure, the substrate **302.1**, in which the 20-ketone is protected as the dimethyl hydrazone derivative, is reacted with a dialkyl phosphonomethyl hydroxylamine **302.8a**,
 10 prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tet. Lett.*, 27:1477 (1986) and BOC-hydroxylamine, to afford the oxime **302.10**. Deprotection, as described in Example 301, then affords the 20-keto phosphonate **302.11**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the
 15 reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether **302.8a**, different oxime ethers **302.2**, the corresponding products **302.4** are obtained.

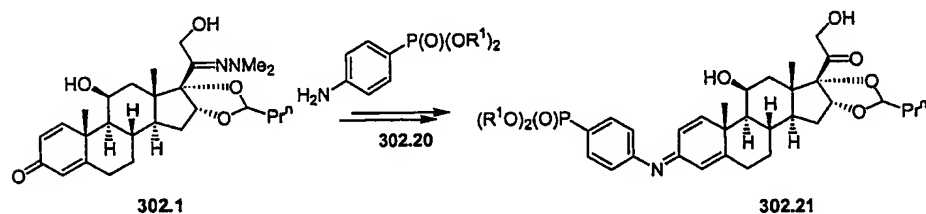


- The synthesis of specific compounds of the invention is shown above.
- The preparation of compounds of the invention in which the phosphonate group is attached by means of a benzyloxy oxime group is illustrated. In this procedure, the dienone **302.1**, in which the 20-ketone is protected as the dimethyl hydrazone, is reacted, as described above, with O-(2-bromobenzyl)hydroxylamine **302.9**, prepared as described above from 2-bromobenzyl bromide and BOC-protected hydroxylamine **302.6**, to give the oxime **302.12**. The protecting group is then removed to yield the 20-keto product **302.13**. The latter product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **302.14** to afford the phosphonate **302.15**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **35**:1371 (1992).
- The reaction is performed at ca. 100° in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

- Alternatively, the bromo compound **302.13** is coupled with a dialkyl vinylphosphonate **302.16** (Aldrich) to afford the phosphonate **302.17**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in "Advanced Organic Chemistry," by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, **12**:146 (1979). The aryl bromide and the olefin are coupled in a polar solvent such as

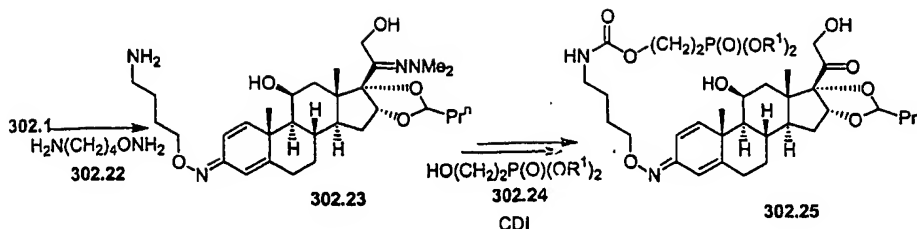
dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product **302.17** is reduced, for example, by reaction with diimide, to produce the saturated analog **302.18**. The reduction of olefinic bonds is described in "Comprehensive Organic Transformations," by R. C. Larock, VCH, 1989, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromobenzyl reagent **302.9**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds **302.15**, **302.17** and **302.18** are obtained.



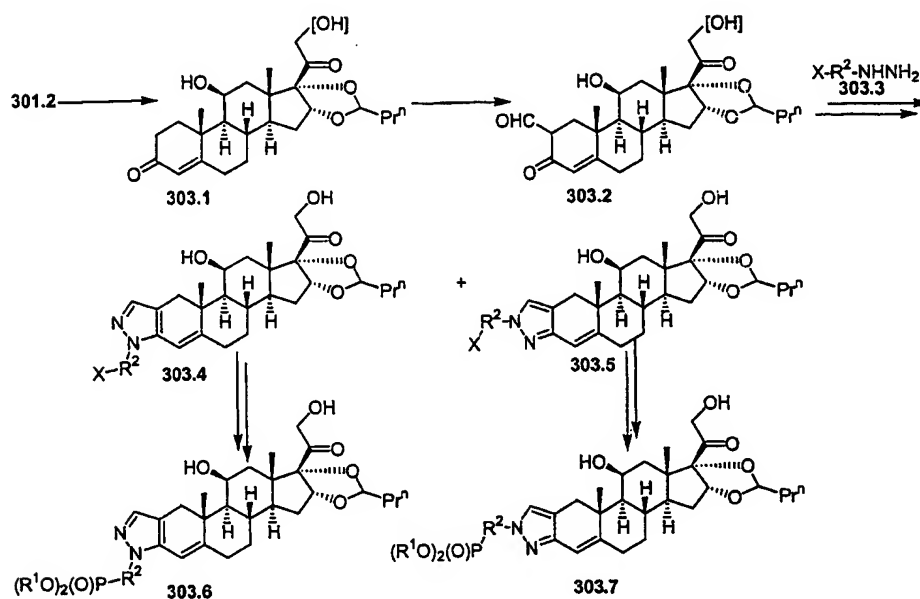
The preparation of specific compounds of the invention is shown above. The preparation of compounds of the invention in which the phosphonate is attached by means of a 4-phenylimino group is illustrated. In this procedure, the substrate **302.1**, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with a dialkyl 4-aminophenyl phosphonate **302.20** (Epsilon), to give, after deprotection, the imine product **302.21**. The imine forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions.

Using the above procedures, but employing, in place of the 4-aminophenyl phosphonate **302.20** different amino-substituted aryl or heteroaryl phosphonates, products analogous to **302.21** are obtained.



The preparation of specific compounds of the invention is shown above. The preparation of compounds of the invention in which the phosphonate is attached by means of an oximino group and a carbamate linkage is illustrated. In this procedure, the dienone 302.1, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with 4-aminobutyl hydroxylamine 302.22 (Pol. J. Chem., 55:1163 (1981)) to yield the oxime 302.23. The reaction of steroidal 1,4-dien-3-ones with hydroxylamines is described in J. Steroid Bioch., 7: 795 (1976). The reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product 302.23 is then coupled with a dialkyl 2-hydroxyethyl phosphonate 302.24 (Epsilon) and carbonyl diimidazole, to yield, after deprotection, the carbamate oxime 302.25. The preparation of carbamates is described in "Comprehensive Organic Functional Group Transformations," A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p 416ff, and in "Organic Functional Group Preparations," by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff. In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate.

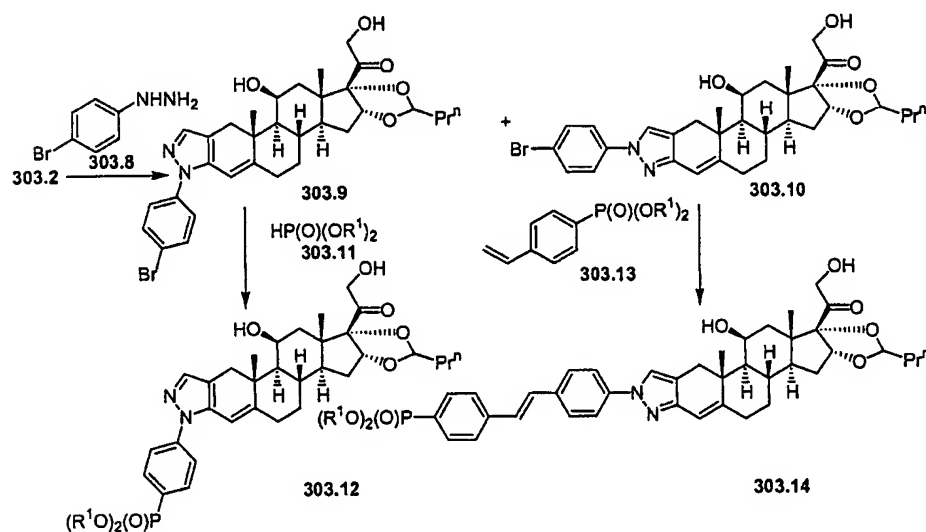
Using the above procedures, but employing, in place of the amino-substituted hydrazine 302.22, different amino-substituted hydrazines, and/or different hydroxy-substituted phosphonates, the products analogous to 302.25 are obtained.

Example 303: Preparation of Representative Budesonide Derivatives

5 The preparation of the phosphonate esters of the invention in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and/or a variable carbon chain is shown above.

In this procedure, the dienone 301.2, in which the 21-hydroxyl group is protected as described in Example 301 is reduced to afford the 1,2-dihydro product 303.1. The catalytic hydrogenation reaction is effected by the use of
 10 tris(triphenylphosphine)rhodium (I) chloride, for example as described in J. Med. Chem., 2001, 44, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or
 15 dimethylformamide, as described in J. Am. Chem. Soc., 1964, 86, 1520, to afford the 2-formyl product 303.2. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine 303.3, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X may be dialkylphosphono,
 20 bromo, hydroxy, amino, carboxyl and the like. The reaction yields, after deprotection of the 21-hydroxyl group, the isomeric 2'- and 1'-aryl pyrazoles

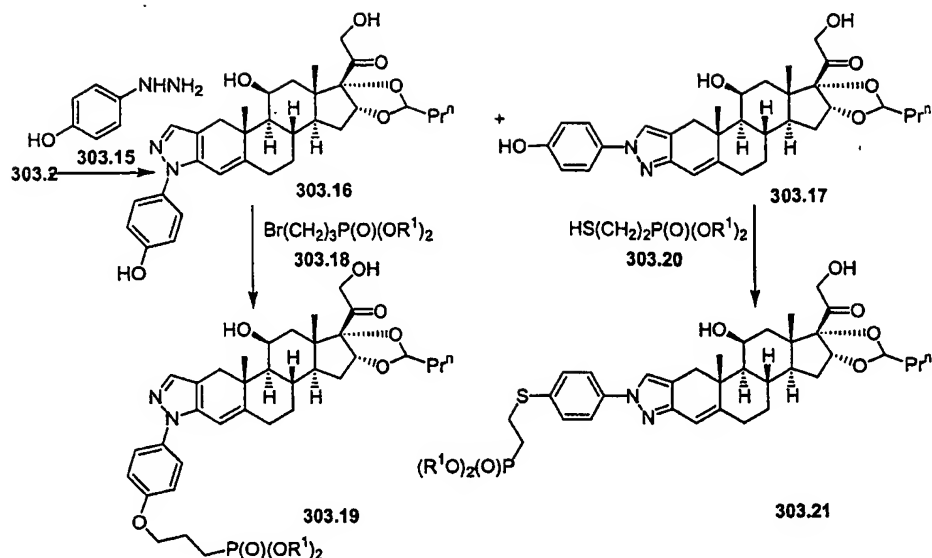
303.4 and 303.5. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in J. Am. Chem. Soc., 1964, 86, 1520. The pyrazoles 303.4 and 303.5 are then transformed, for example by the procedures described herein, into the phosphonates 303.6 and 303.7.



The preparation of specific compounds of the invention is illustrated above. The preparation of phosphonates of the invention in which the phosphonate is attached by means of a phenyl ring or a stilbene moiety is shown. In this procedure, the ketoaldehyde 303.2 is reacted, as described above, with 4-bromophenyl hydrazine 303.8 (J. Organomet. Chem., 1999, 62, 581) to give the pyrazoles 303.9 and 303.10. The 2'-substituted isomer 303.9 is then reacted, as described above, with a dialkyl phosphite 303.11 to give the phosphonate 303.12.

The isomeric pyrazole 303.10 is reacted in a Heck reaction, as described above, with one molar equivalent of a dialkyl 4-vinylphenyl phosphonate 303.13 (Macromolecules, 1998, 31, 2918) to yield the phosphonate 303.14.

Using the above procedures, but employing different bromo-substituted hydrazines, and/or different alkenyl-substituted phosphonates, the products analogous to 303.12 and 303.14 are obtained.



The synthesis of specific compounds of the invention is shown above.

- 5 The preparation of the phosphonates of the invention in which the phosphonate group is attached by means of an alkoxy or alkylthio group and an aromatic ring is illustrated. In this procedure, the ketoaldehyde 303.2 is reacted, as described above, with 4-hydroxyphenyl hydrazine 303.15 (EP 437105) to produce the pyrazoles 303.16 and 303.17. The 2'-substituted isomer 303.16 is then reacted in
- 10 dimethylformamide solution at 70° with one molar equivalent of a dialkyl bromopropyl phosphonate 303.18 (J. Amer. Chem. Soc., 2000, 122, 1554) and cesium carbonate, to give the ether phosphonate 303.19.

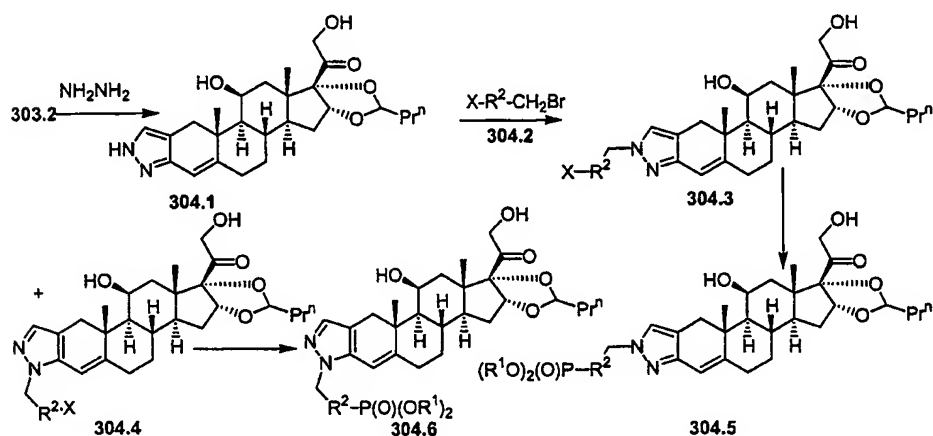
- Alternatively, the 1'-substituted pyrazole 303.22 is coupled in a Mitsunobu reaction, with a dialkyl 2-mercaptoethyl phosphonate 303.20 (Zh.
- 15 Obschei. Khim., 1973, 43, 2364) to prepare the thioether phosphonate 303.21. The preparation of aromatic ethers and thioethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React.,
- 20 1992, 42, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the

presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656.

Using the above procedures, but employing, in place of the
 5 hydroxyphenyl hydrazine **303.15**, different hydroxyaryl hydrazines, and/or different dialkyl bromo- or mercapto-substituted phosphonates, the products analogous to the compounds **303.19** and **303.21** are obtained.

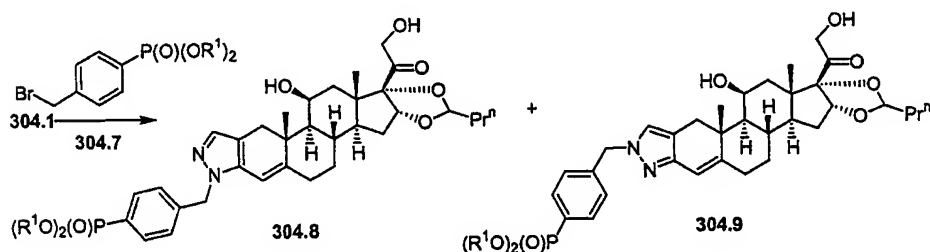
Example 304: Preparation of Representative Budesonide Derivatives

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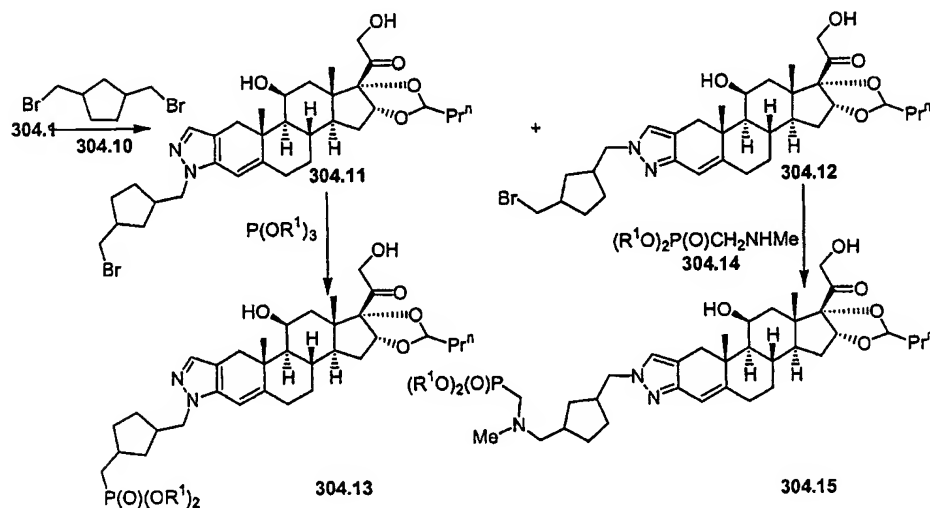
The preparation of the phosphonate esters of the invention in which the phosphonate group is attached by means of a variable carbon linkage is shown above. In this procedure, the ketoaldehyde **303.2** is reacted with hydrazine to
 15 afford the pyrazole derivative **304.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in J. Am. Chem. Soc, 1964, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound **304.2**, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the
 20 alkylation products **304.3** and **304.4**. The alkylation of substituted pyrazoles is described, for example, in Heterocyclic Chemistry, by T. L. Gilchrist, Longman, 1992, p. 309. The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium

hexamethyldisilazide and the like. The products **304.3** and **304.4** are, except in cases where *X* is dialkylphosphono, converted into the phosphonates **304.5** and **304.6**, using the procedures described herein.



5

The preparation of specific compounds of the invention is shown above. The pyrazole **304.1** is reacted in dimethylformamide solution at 70° with one molar equivalent of a dialkyl 4-bromomethylphenyl phosphonate **304.7** (Tet., 1998, 54, 9341) and lithium hexamethyl disilazide, to give the pyrazoles **304.8** and **304.9**. Using the above procedures, but employing different bromomethyl-substituted phosphonates, the products analogous to **304.8** and **304.9** are obtained.



15

The preparation of specific compounds of the invention is shown above. The pyrazole **304.1** is reacted in tetrahydrofuran solution with 1,3-bis(bromomethyl)cyclopentane **304.10** (Bull. Soc. Chim. Fr., 1975, 1295) and

sodium hydride, to give the alkylation products **304.11** and **304.12**. The 2'-substituted isomer **304.11** is then reacted, in a Arbuzov reaction, with a trialkyl phosphite to yield the phosphonate **304.13**. The Arbuzov reaction is described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, in which a
5 bromo substituent is converted into the corresponding phosphonate, the substrate is heated at from about 60° to about 160° with a five to fifty-fold molar excess of a trialkyl phosphite, to effect the transformation.

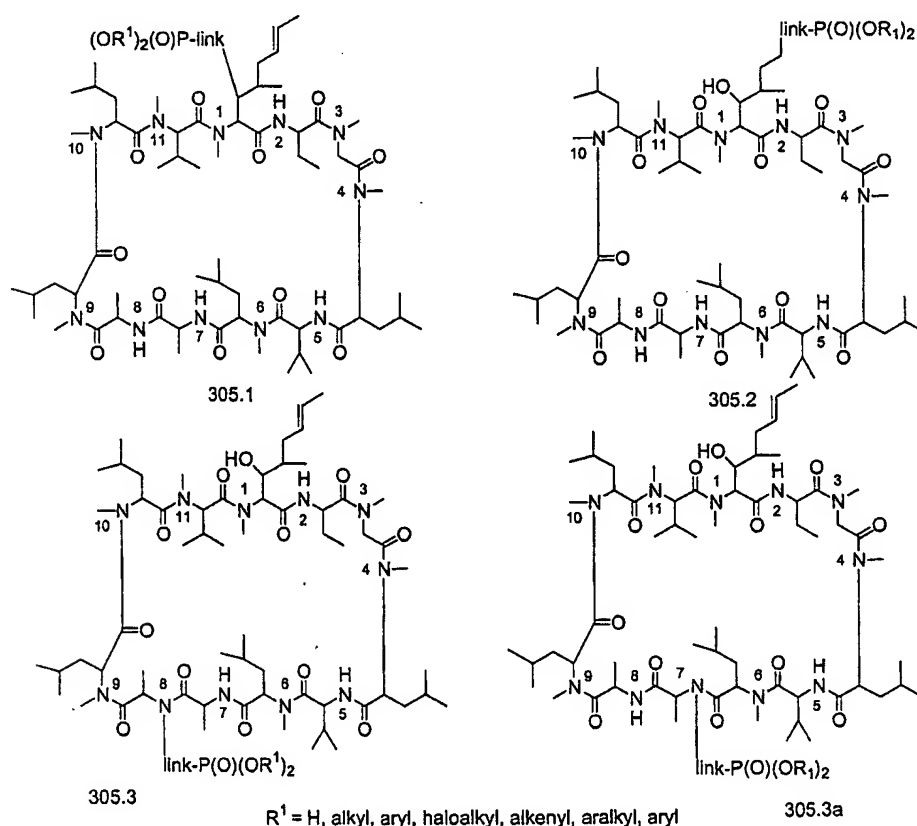
The 2'-substituted pyrazole **304.12** is reacted at 70° in dimethylformamide solution with one molar equivalent of a dialkyl
10 methylaminomethyl phosphonate **304.14** (AsInEx) and cesium carbonate, to give the amine phosphonate **304.15**.

Using the above procedures, but employing different dihalides, and/or different amino-substituted phosphonates, the products analogous to **304.13** and **304.15** are obtained.

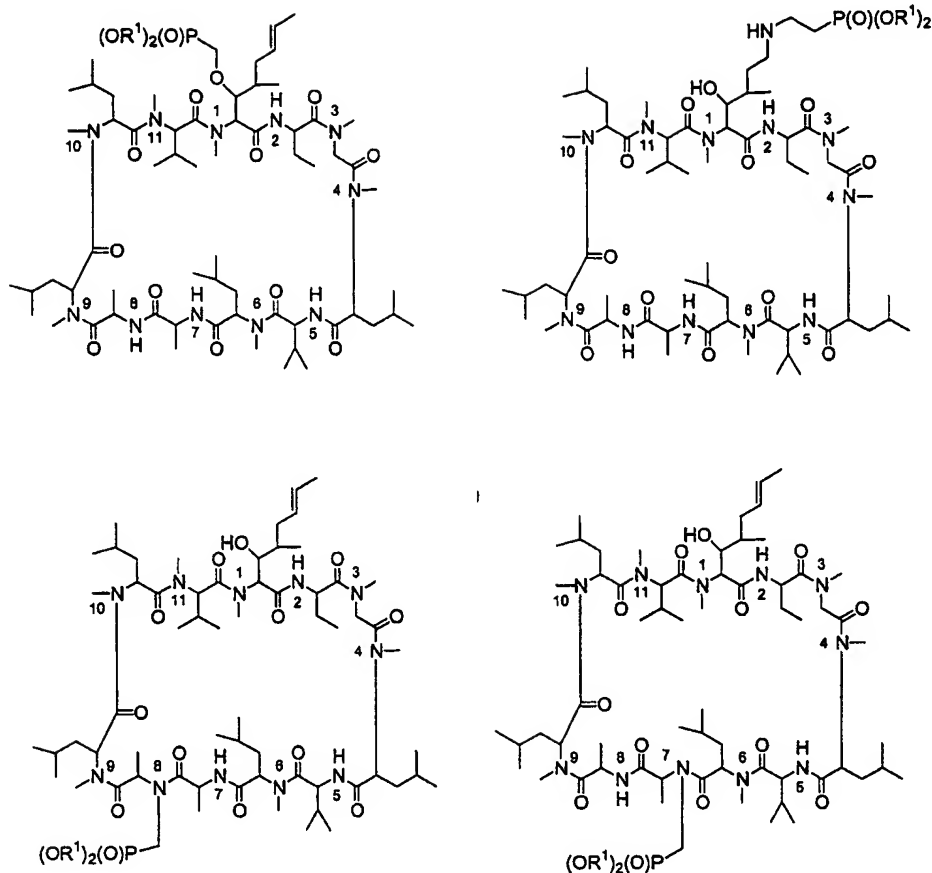
15

Example 305: Preparation of Representative Cyclosporin A Derivatives

In general, phosphonate interconversions of the compounds of the invention, as described in Examples 305-308, can be performed as described herein. The final compounds are synthesized according to the methods described herein. Exemplary intermediate phosphonate esters, *e.g.*, **305.1**, **305.2**, **305.3** and **305.3a**, are shown below and these compounds can be used to prepare final compounds, such as those illustrated below, by one skilled in the art, using known methods for synthesis of substituted phosphonates. These methods are similar to those described for the synthesis of amides. The preparation of amides from carboxylic acids and derivatives is described, for example, in "Organic Functional Group Preparations," by S.R. Sandler and W. Karo, Academic Press, 1968, p. 274. Further methods are described below for the synthesis of the phosphonate diesters and can in some cases be applied to the synthesis of phosphor-amides.



15



In the following schemes, the conversion of various substituents into the group link-P(O)(OR¹)₂, where R¹ is defined as above, or indeed the final stage of P(O)RR^o, as defined above, can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, amino, during the introduction of the group link-P(O)(OR¹)₂ or P(O)RR^o.

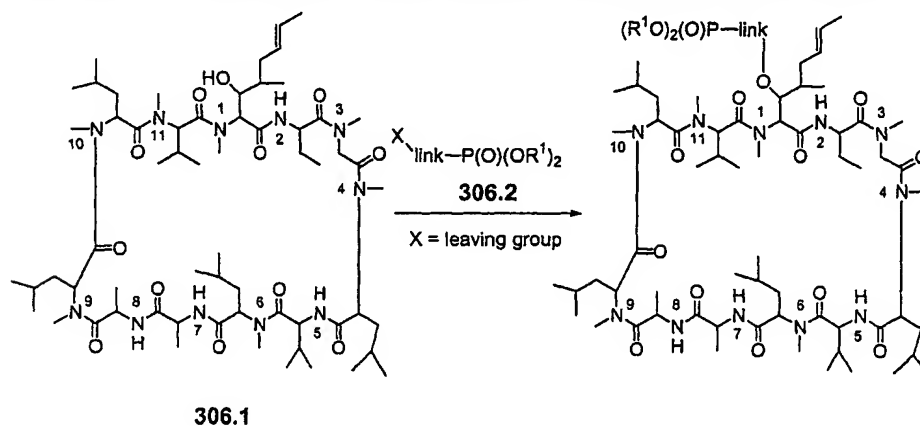
In the succeeding examples, the nature of the phosphonate ester group P(O)(OR¹)₂ can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below.

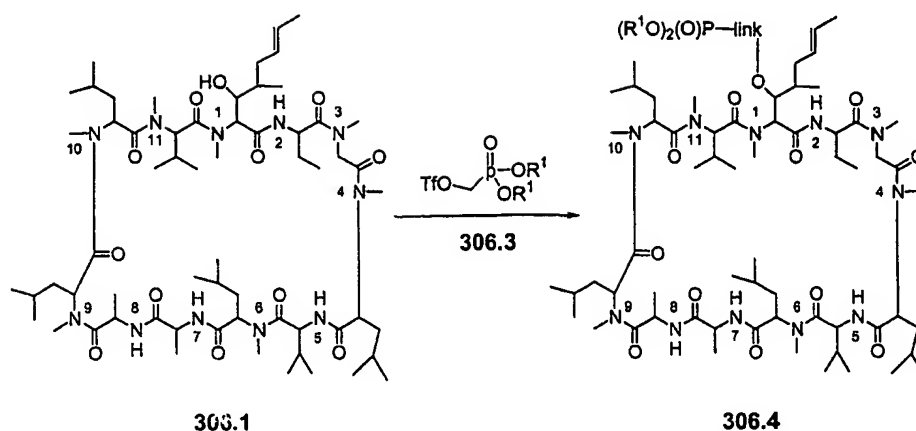
Protection of reactive substituents

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Third Edition 1999. Reactive substituents, which may be protected, are shown below as, for example, [OH], [SH], *etc.*

Preparation of Intermediate Phosphonates

The intermediate phosphonate esters **305.1-305.3a** involved in conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown above. Cyclosporin A (CsA) can be purchased from Sigma Aldrich, synthesized (see U.S. Patent No. 4,396,542) or obtained from biological sources as described in U.S. Patent No. 4,117,118. Other cyclosporin derivatives can be either synthetic in nature (see U.S. Patent No. 4,396,542) or isolated by similar means to CsA (see U.S. Patent No. 6,410,696 B1).

Example 306: Preparation of Representative Cyclosporin A Derivatives

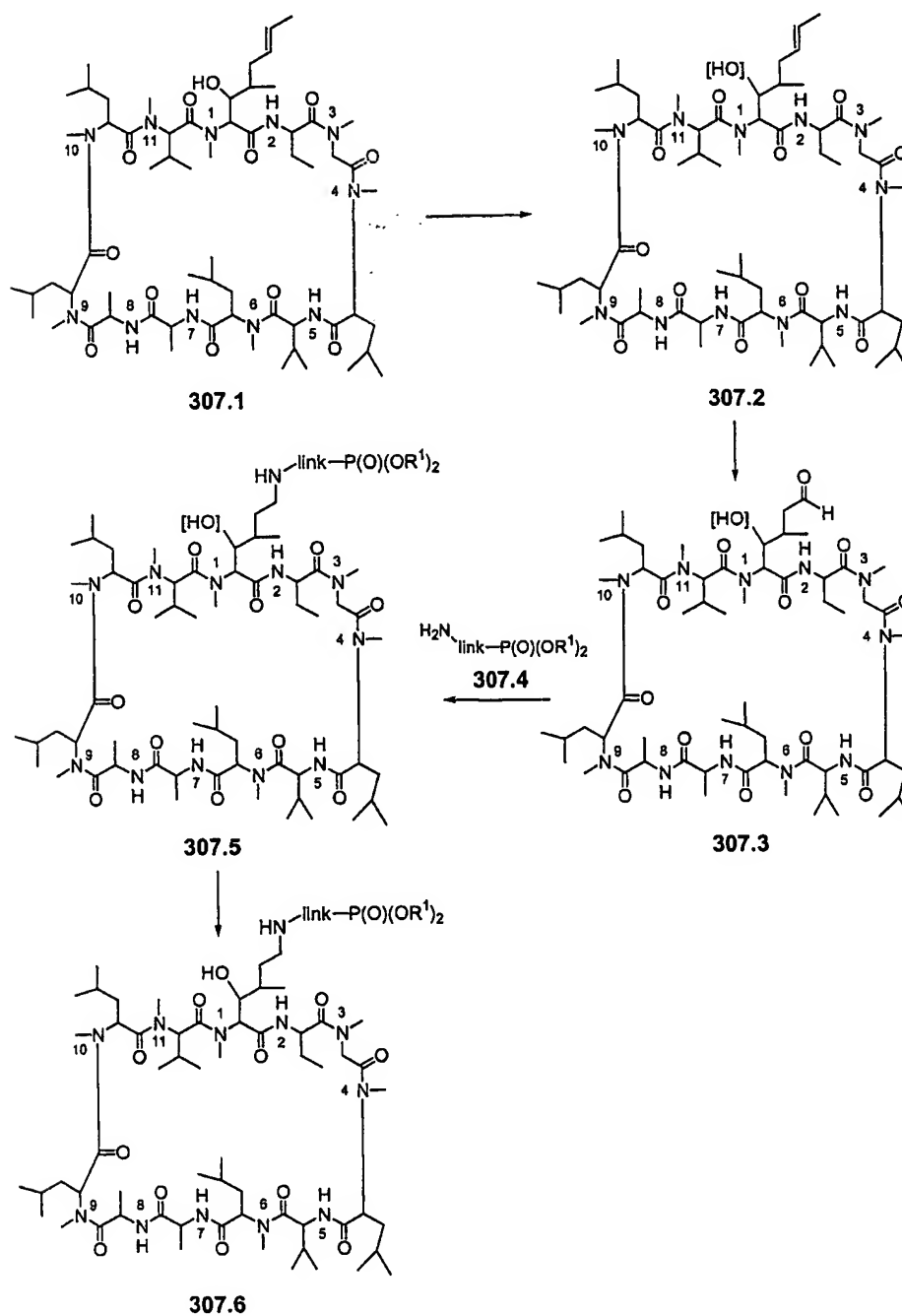


The preparation of the phosphonate linkage to CsA through the hydroxyl group of amino acid 1 to give compounds of the invention is shown above. CsA

5 **306.1** is dissolved in a suitable solvent such as, for example, DMF or other non-protic solvent, and is then treated with the phosphonate reagent **306.2**, bearing a leaving group, for example, bromine, mesyl, tosyl, or trifluoromethanesulfonyl in the presence of a suitable organic or inorganic base. For example, **306.1** dissolved in DMF, is treated with one equivalent of sodium hydride and one

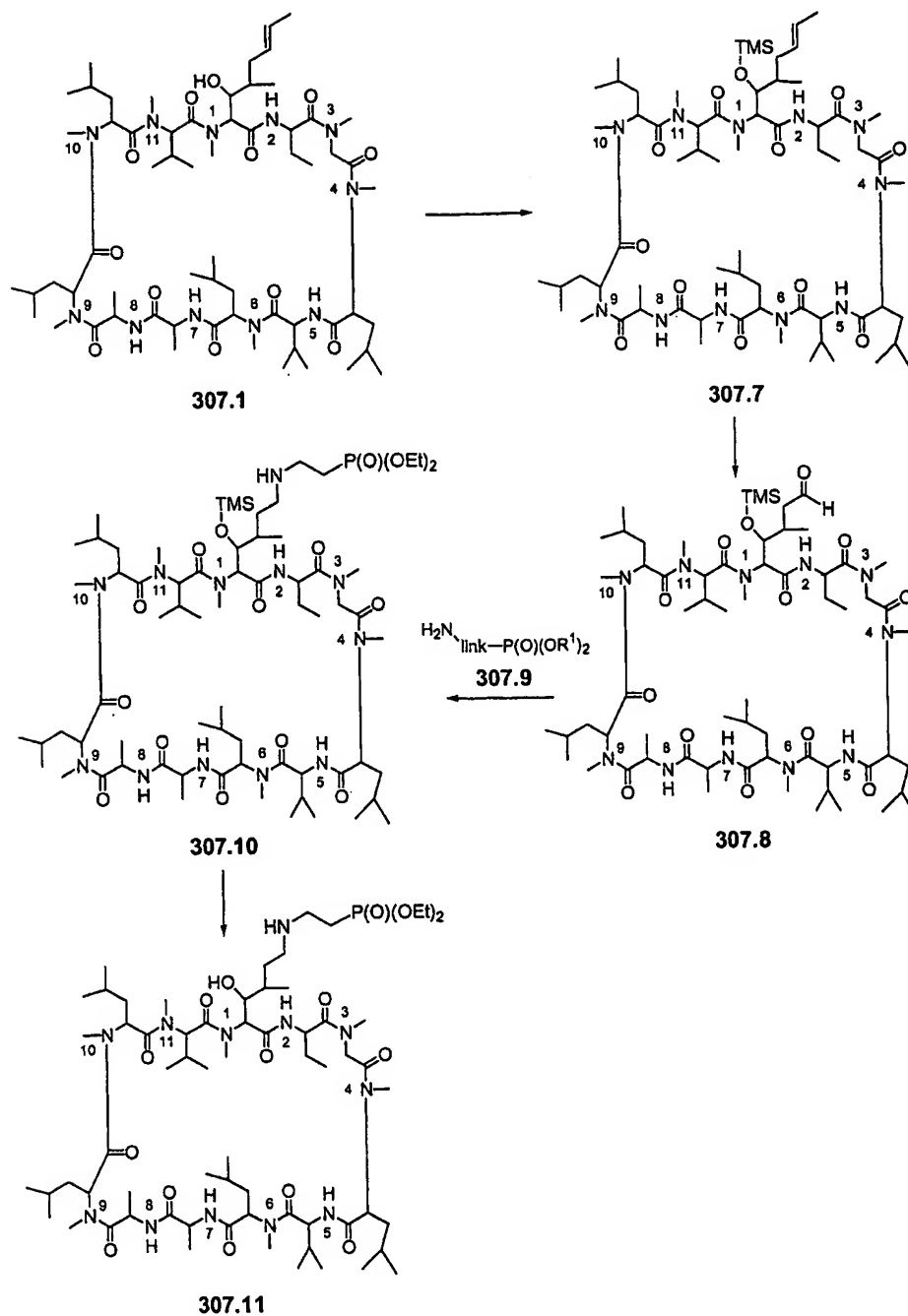
10 equivalent of (toluene-4-sulfonylmethyl)-phosphonic acid dibenzyl ester **306.3**, prepared according to the procedures in JOC 1996, 61,22, p7697, to give CsA phosphonate **306.4**. Using the above procedure but employing different phosphonate reagents **306.2** in place of **306.3** there are obtained the corresponding products of the invention bearing different linking groups.

15

Example 307: Preparation of Representative Cyclosporin A Derivatives

5 The preparation of CsA - phosphonate conjugates of the invention is illustrated above. The hydroxyl group of amino acid 1 is first protected with a

suitable protecting group, for example silyl ethers, benzyl ethers, trityl ethers etc as described in Greene and Wuts, "Protecting Groups in Organic Synthesis," 3rd Edition, John Wiley and Sons. The protected product 307.2 is then treated with an oxidizing agent, many examples of which are described in Comprehensive
5 Organic Transformations, John Wiley & Sons, 2nd Ed, R. C. Larock, p 1211-1215 to give the aldehyde. Aldehyde 307.3 is then treated with a amine phosphonic acid ester of the general formula 307.4 under reductive amination conditions to afford amine 307.5. The preparation of amines by means of reductive amination procedures is described, for example, in "Comprehensive
10 Organic Transformations," by R. C. Larock, 2nd edition, p. 835. In this procedure, the amine component and the aldehyde component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product. Finally, deprotection of the hydroxyl group following procedures
15 documented in Greene and Wuts, "Protecting Groups in Organic Synthesis," 3rd Edition, John Wiley and Sons, p116-121 gives the phosphonate.

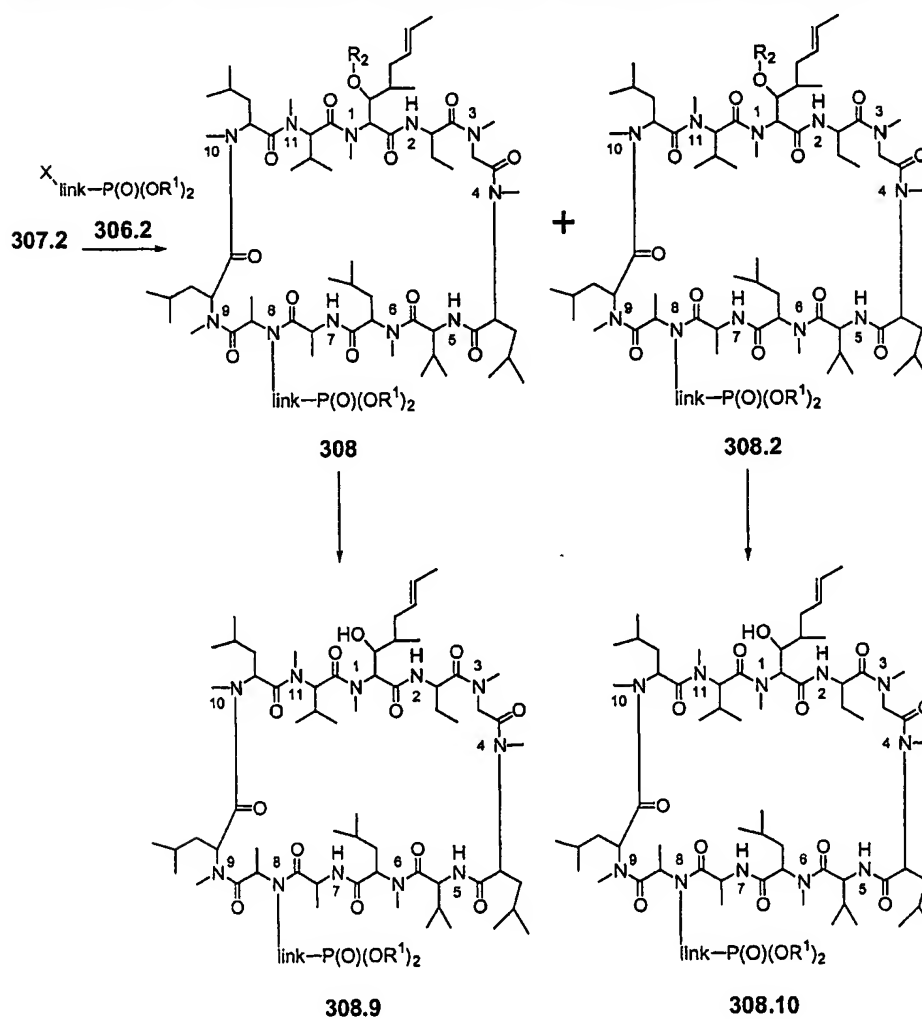


For example, 307.1 is treated in pyridine and dichloromethane with trimethylsilyl chloride, as described in U.S. Patent No. 6,410,696 B1, to give
 5 silyl ether 307.5. Silyl ether 307.5 is then treated with ozone followed by work up with dimethyl sulfide to give aldehyde 307.8. Aldehyde 307.8 is treated with

one equivalent of the hydrochloride salt of (2-amino-ethyl)-phosphonic acid ester diethyl ester **307.9**, prepared according to J. Med. Chem. 1998, 41, 23, p4439, and a suitable base, *e.g.*, hunigs base, triethylamine, or the likes, until the imine is formed. The intermediate imine solution is then treated with sodium cyanoborohydride to give the amine **307.10**. Amine **307.10** is then deprotected by treatment with TBAF in an aprotic solvent such as THF or dioxane to give phosphonate **307.11**. Using the above procedure but employing different phosphonate reagents **307.4** in place of **307.9** there are obtained the corresponding products bearing different linking groups.

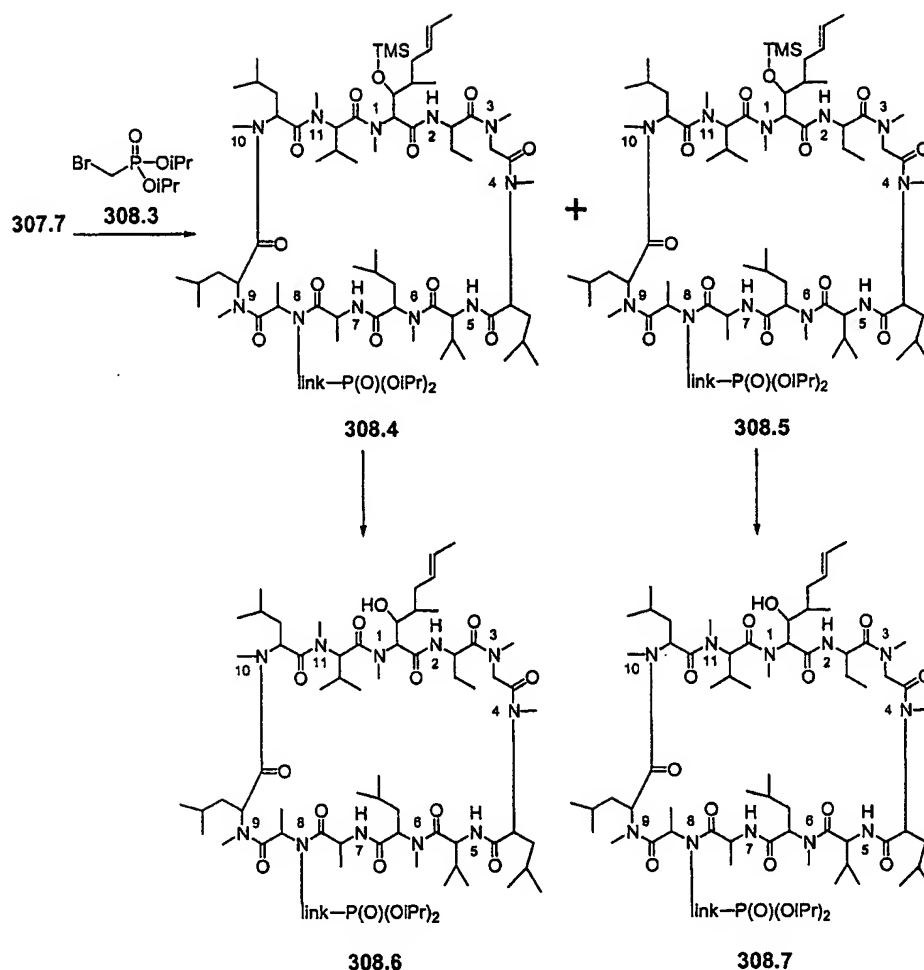
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Example 308: Preparation of Representative Cyclosporin A Derivatives



The preparation of CsA phosphonate conjugates of the invention whereby the phosphonate is linked onto the alanine nitrogen in amino acids 7 and 8 is shown above. Protected CsA 307.2 (Example 307) is first treated with a base, sufficiently basic to remove the amide proton, for example, metal hydrides, metal amides. The product is then treated with a phosphonate reagent 306.2 bearing a leaving group such as, for example, bromine, mesyl, tosyl, or trifluoromethanesulfonyl phosphonates, to give 308.1 and 308.2. The alkylated products are then separated by chromatography and independently deprotected using conventional conditions described in Greene and Wuts, Protecting groups in Organic Synthesis, 3rd Edition, John Wiley and Sons inc. p116-121 to give compounds of the invention. For example, silyl ether 307.5, in toluene is treated with sodium hydride and 15-crown-5-ether followed by one equivalent of bromomethyl phosphonic acid diallyl ester, 308.3 (Lancaster), to give phosphonates 308.4 and 308.5, respectively. Phosphonates 308.4 and 308.5 are then deprotected by treatment with TBAF in an aprotic solvent such as THF or dioxane to give 308.6 and 308.7, respectively, in which the linkage is a methylene group. Using the above procedure, but employing different phosphonate reagents 306.2 in place of 308.3, there are obtained the corresponding products with different linking groups.

20

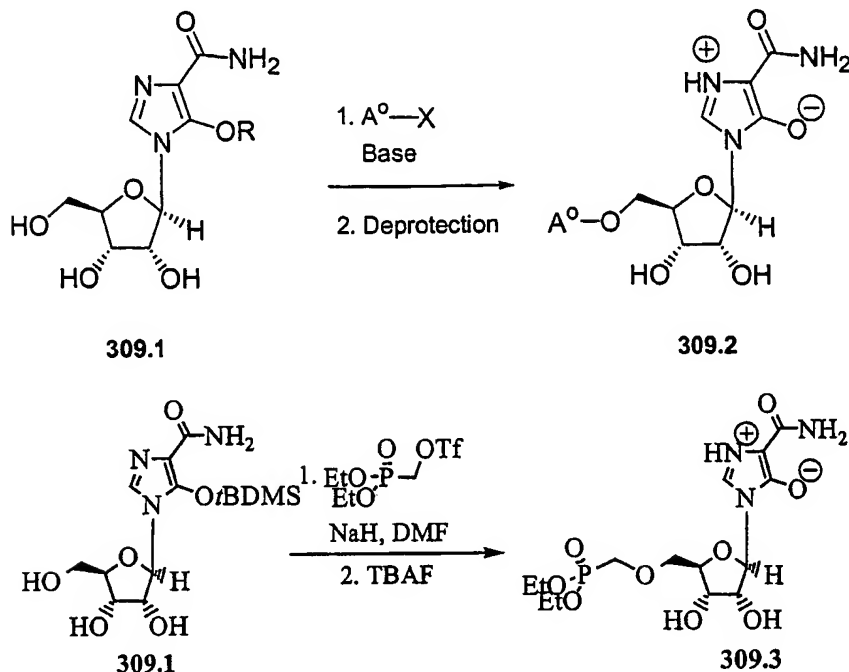


Example 309: Preparation of Representative Mizoribine Derivatives

Representative compounds of the invention may be prepared according to the following methods.

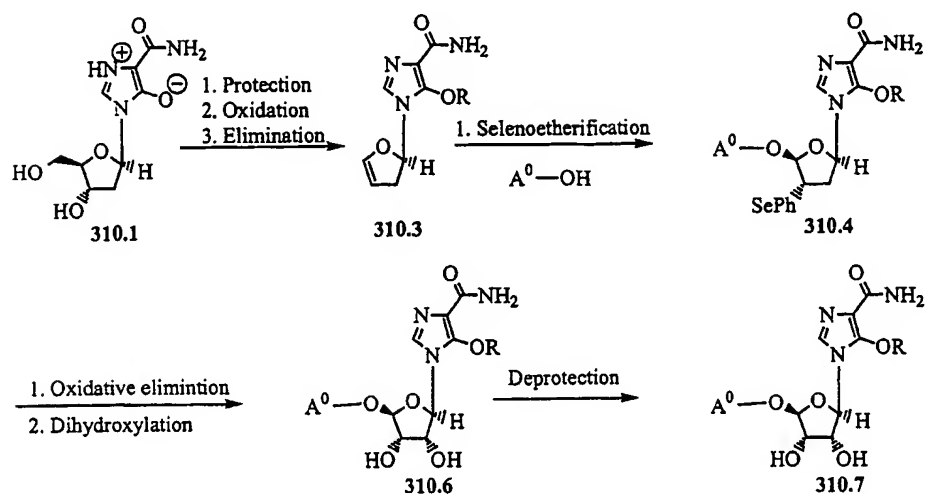
Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis (Second Edition, Wiley, 1991). The protection and deprotection of steroidal ketones is described in J. Fried and J. A. Edwards, Organic Reactions in Steroid Chemistry, Vol. 1 375ff (van

Nostrand Reinhold, 1972). Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [O], *etc.*

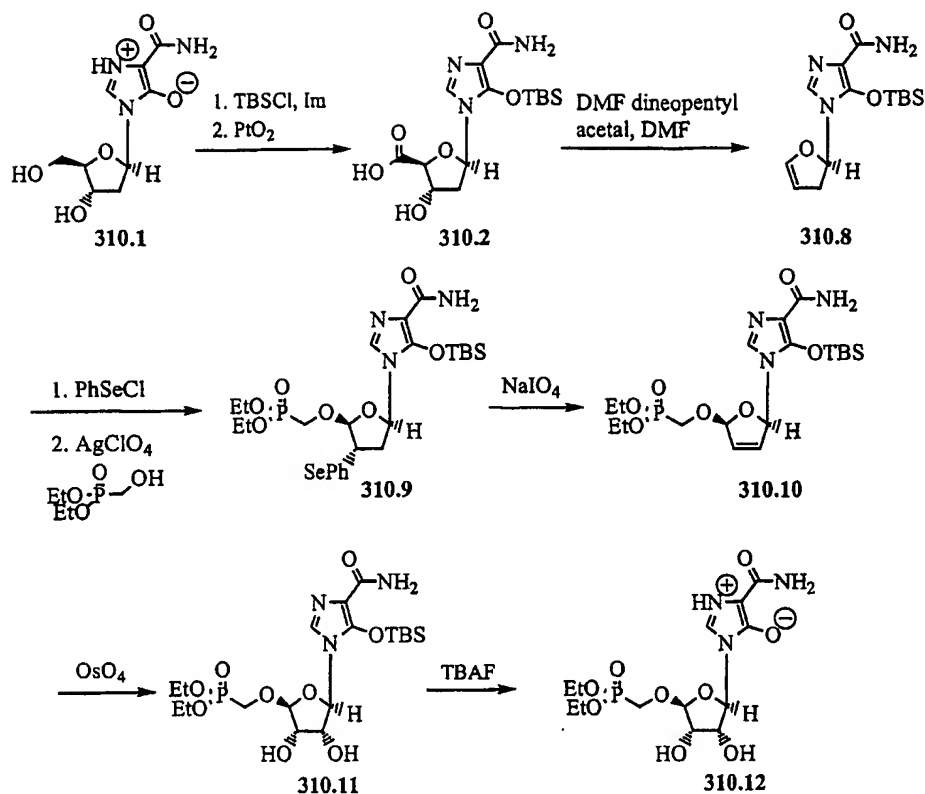


5

Depicted above is the preparation of phosphonates of the invention. The 5-hydroxy-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamide **309.1** (prepared according to U.S. Patent No. 3,888,843) can be treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, **1986**, 27, 1477) is added, yielding the desired phosphonate diester **309.2**, *e.g.*, **309.3**.

Example 310: Preparation of Representative Compounds of Mizoribine

- 5 The preparation of the phosphonate esters of the invention is depicted above. Compound **310.1**, 5-hydroxy-1-(4-hydroxy-5-hydroxymethyl-tetrahydrofuran-2-ylmethyl)-1H-imidazole-4-carboxylic acid amide can be prepared by addition of the imidazole base (JP Kokai 76 88965) onto the 3,5-bis-protected 2-deoxy-D-*erythro*-pentofuranosyl chloride (Hayashi, M. et al., *Chem. Pharm.*
- 10 *Bull.*, **1975**, 23, 1, 245; Montgomery, J. A. et al., *J. Med. Chem.*, **1969**, 12, 3, 498; and Iwamoto, R. H. et al., *J. Med. Chem.*, **1963**, 6, 684). Compound **310.1** is then protected on the imidazol-4-ol. Oxidation of the 5'-OH followed by elimination provides glycal **310.3** (see the procedure of Zemlicka J. et al., *J. Am. Chem. Soc.*, **1972**, 94, 9, 3213). Selenoetherification provides the protected
- 15 phosphonate **310.4** (Kim, C. et al., *J. Org. Chem.*, **1991**, 56, 2642). Oxidative elimination of the phenylselenide (as described in Kim, C. et al., *J. Org. Chem.*, **1991**, 56, 2642) followed by stereoselective dihydroxylation provides the diol **310.6**. Finally, the protecting group is removed to provide **310.7**.



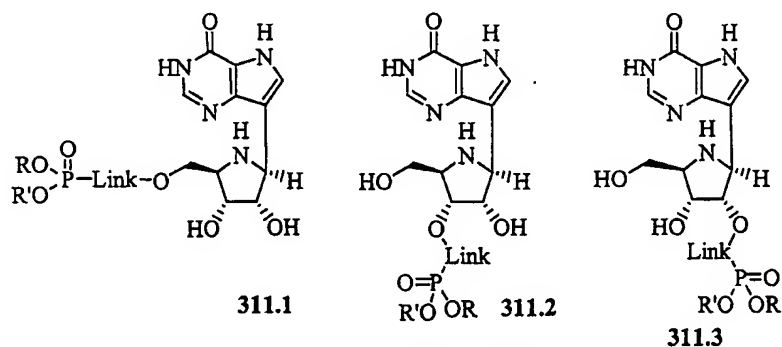
Illustrated above is the preparation of specific compounds of the invention. Specifically, compound 310.1, 5-hydroxy-1-(4-hydroxy-5-hydroxymethyl-tetrahydrofuran-2-ylmethyl)-1H-imidazole-4-carboxylic acid amide, which can be prepared by addition of the imidazole base (JP Kokai 76 88965; also Schipper, E. et al., *J. Am. Chem. Soc.*, **1952**, 74, 350) onto the 3,5-bis-protected 2-deoxy-D-erythro-pentofuranosyl chloride (Hayashi, M. et al., *Chem. Pharm. Bull.*, **1975**, 23, 1, 245; Montgomery, J. A. et al., *J. Med. Chem.*, **1969**, 12, 3, 498; and Iwamoto, R. H. et al., *J. Med. Chem.*, **1963**, 6, 684) is first protected using a TBS group. Subsequent oxidation with PtO₂ proceeds to provide carboxylic acid 310.2. Decarboxylative elimination is achieved using dimethylformamide dineopentyl acetal in DMF at high temperature (Zemlicka J. et al., *J. Am. Chem. Soc.*, **1972**, 94, 9, 3213). Once the furanoid glycal 310.8 is in hand, it is treated with silver perchlorate in the presence of diethyl(hydroxymethyl)phosphonate (Phillion, D. et al., *Tetrahedron Lett.*,

1986, 27, 1477) to provide the phosphonate **310.9** (Kim, C. et al., *J. Org. Chem.*, **1991**, 56, 2642). Oxidative elimination of the selenide followed by dihydroxylation using osmium tetroxide provides a diol with the desired stereochemistry. Deprotection of the TBS group can be achieved using TBAF.

5

Example 311: Preparation of Representative BCX-1777 Derivatives

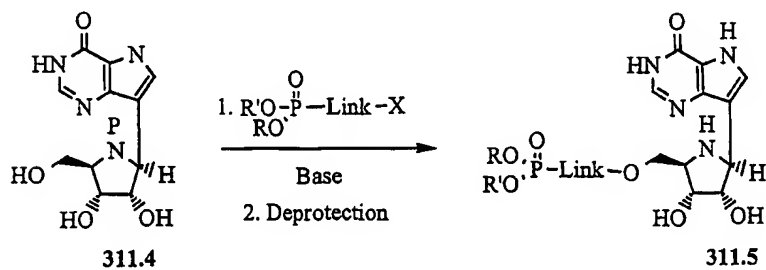
In general, the preparation of the following representative compounds of the invention is illustrated below.



Link is 1-8 atoms in length,
with 2-6 atoms preferred

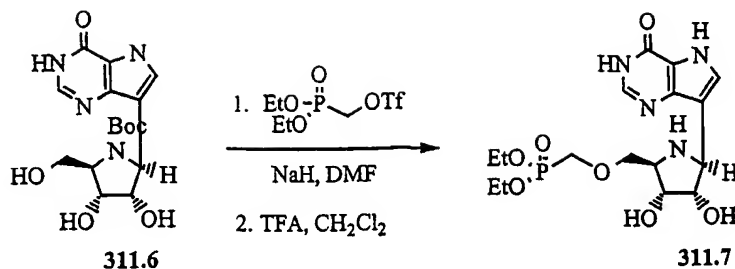
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Compounds of the invention such as **311.5** can be made according to the general route outlined below.



15

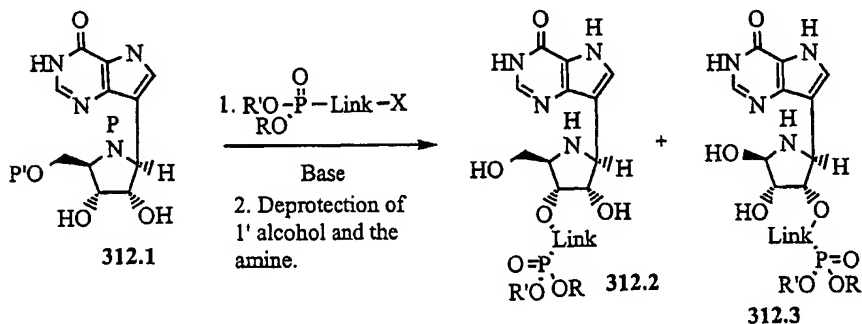
A specific compound of the invention may be prepared as follows:



The Boc-protected (1S)-1-(9-deazaguanin-9-yl)-1,4-dideoxy-1,4-imino-D-ribose, compound 311.6, is prepared by stirring the (1S)-1-(9-deazaguanin-9-yl)-1,4-dideoxy-1,4-imino-D-ribose (WO 9,919,338 and Evans, G. B. et al., *Tetrahedron*, 2000, 56, 3053, also reported in Evans, G. B. et al., *J. Med. Chem.* 2003, 46, 3412) with BOC anhydride as described in Greene, T., *Protective groups in organic synthesis*, Wiley-Interscience, 1999. Compound 311.6 is then treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, 1986, 27, 1477) is added, yielding the desired phosphonate 311.6 after deprotection of the BOC group using trifluoroacetic acid (TFA).

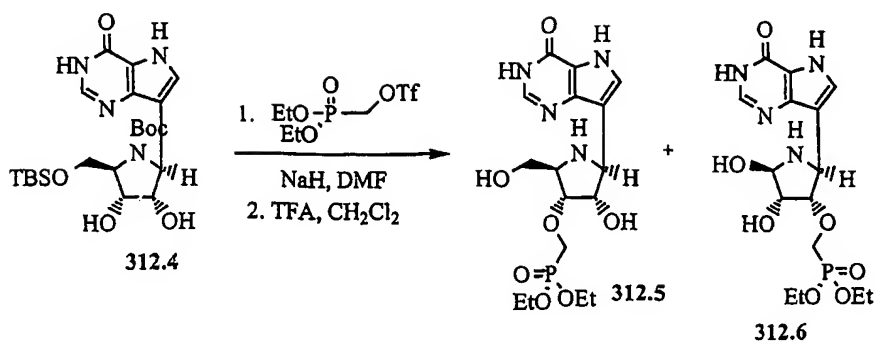
Example 312: Preparation of Representative BCX-1777 Derivatives

The preparation of representative compounds of the invention are shown below. Compounds such as 312.2 and 312.3 can be made according to the general route outlined below.



20

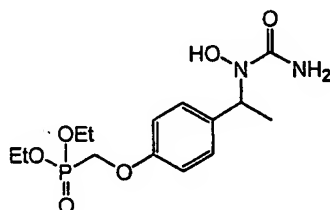
A specific compound of the invention can be prepared as follows:



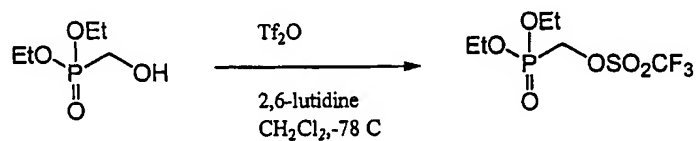
The Boc-protected (1S)-1-(9-deazaguanin-9-yl)-1,4-dideoxy-1,4-imino-D-ribose, compound **312.4**, is prepared by stirring the (1S)-1-(9-deazaguanin-9-yl)-1,4-dideoxy-1,4-imino-D-ribose (WO 9,919,338 and Evans, G. B. et al., *Tetrahedron*, **2000**, *56*, 3053, also reported in Evans, G. B. et al., *J. Med. Chem.* **2003**, *46*, 3412) with BOC anhydride as described in Greene, T., "Protective Groups in Organic Synthesis," Wiley-Interscience, 1999. Subsequent protection of the primary alcohol using a TBS group can be achieved using TBSCl and imidazole in solvents such as CH₂Cl₂ as described in Greene, T. "Protective Groups in Organic Synthesis," Wiley-Interscience, 1999 to provide compound **312.1**. Compound **312.1** is then treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, **1986**, *27*, 1477) is added, yielding a mixture of the desired phosphonate diester **312.2** and **312.3** after deprotection of the BOC group using trifluoroacetic acid (TFA). Compounds **312.2** and **312.3** can be also prepared *via* a more complicated 2' OH protected analog of **312.1** followed by alkylation using the diethyl phosphonomethyltriflate to provide compound **312.2** exclusively. Compound **312.3** can also be prepared by installation of a different protecting group at the 3' OH position, followed by deprotection of 2' OH and alkylation with diethyl phosphonomethyltriflate at the 2' center followed by global deprotection.

Example 313: Preparation of Representative Zileuton Compounds of the Invention.

Specific compounds of the invention can be prepared as follows:



Diethyl(trifluoromethanesulfonyloxy)methylphosphonate

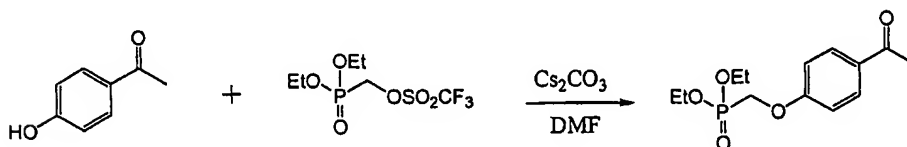


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To a solution of diethyl hydroxymethylphosphonate (14.0g, 83.27 mmol) and 2,6-lutidine (10.7g, 99.9 mmol) in DCM (80 mL) at -78 °C was added triflic anhydride (25.83g, 91.5 mmol), dropwise, and the solution was stirred for 15 minutes. The resulting mixture was then warmed to 0 °C, stirred for 30 minutes, and diluted with ethyl acetate. The mixture was sequentially washed with 1N HCl, saturated NaHCO₃, and brine and then concentrated. The residue was purified by silica column chromatography (3:2 hexane/ethylacetate), affording the desired product as a clear yellowish oil. Yield (18.8 g, 75%) MS m/z (MH)⁺ 301.

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(4-Acetyl-phenoxy)methyl)-phosphonic acid diethyl ester

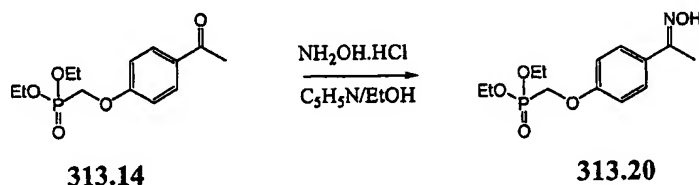


A reaction mixture of 4-hydroxyacetophenone (1.58g, 11.10mmol), trifluoromethanesulfonic anhydride (3.66g, 12.2 mmol) and cesium carbonate (4.34g, 13.32 mmol) in DMF (55mL) was stirred overnight at room temperature. The reaction mixture was diluted with water (100 mL) and the product was
5 extracted with ethyl acetate (2x100 mL), washed with water and brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with ethyl acetate/hexane (2:3), to yield the product (4.6 g, 78%).

MS m/z (MH)⁺ 287.

10

Preparation of Oxime (313.20)

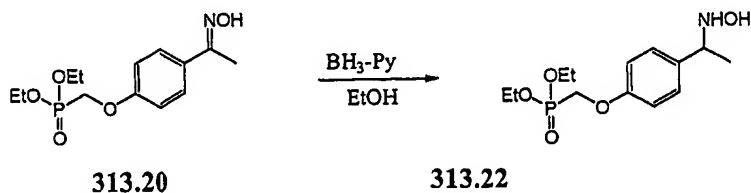


15

A mixture of **313.14** (1.5g, 5.24 mmol), hydroxylamine hydrochloride (0.437g, 6.28 mmol), pyridine (15 mL) and ethanol (15 mL) was stirred at room temperature for two days. The reaction mixture was concentrated to dryness, taken up in ether (20 mL) and washed with 3N HCl. The organic layer was dried
20 over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting solid was purified chromatography on silica gel, eluting with CHCl₃:MeOH (98:2), to yield the desired product (1.1 g, 68%).

MS m/z (MH)⁺ 301.

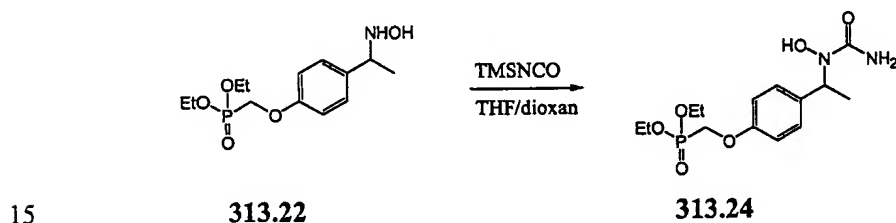
25 Reduction of oxime (313.22)



Oxime (313.20) (0.3 g, 1 mmol) was dissolved in ethanol (10 mL) and freshly-prepared $\text{BH}_3\text{-Py}$ complex (1 mL) was added. The solution was stirred for 10 minutes at room temperature, whereupon 6 N HCl (1.8 mL) was added, dropwise. Further stirring was continued for 1 hour at room temperature. The reaction mixture was then brought to pH 8-9 by addition of 2N NaOH. The product was extracted with ethyl acetate (2x50 mL), dried over anhydrous sodium sulfate and concentrated to yield a viscous liquid (0.32 g) which contained some residual pyridine but was suitable for use in the next step.

MS m/z (MH)⁺ 303.

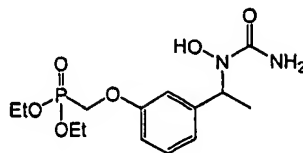
Synthesis of N-hydroxy urea (313.24)



To a solution of 313.22 (0.3g, 1 mmol) in 1,4-dioxane (5 mL) and THF (5 mL) was added trimethylsilyl isocyanate (0.16 mL, 1.2 mmol). The reaction mixture was heated at 90 °C for 1 h, cooled to room temperature and poured into a ice-cooled saturated solution of ammonium chloride. The product was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with $\text{CHCl}_3\text{-MeOH}$, (96:4) to give the desired product (0.14 g, 40%). MS m/z (MH)⁺ 347. ¹H NMR (CDCl_3) δ 1.32-1.37 (m, 6H, CH_3) 1.48-1.51 (d, 3H, CH_3 , 4.13-4.23 (m, 6H, $-\text{CH}_2-$, $-\text{CH}_2-$, $\text{OCH}_2\text{-P}$) 5.3-5.4 (m, 3H, $-\text{CH}-$, NH_2), 6.86-7.35 (m, 4H, C_6H_4), 8.29 (1H, N-OH). HPLC Purity 79 % major 16% minor (sphereclone 5 μL , H_2O : MeCN, 20 minute linear gradient from 10-90% MeCN, 1.0 mL/min). ³¹P NMR (CDCl_3) δ 19.75-20.17, m.

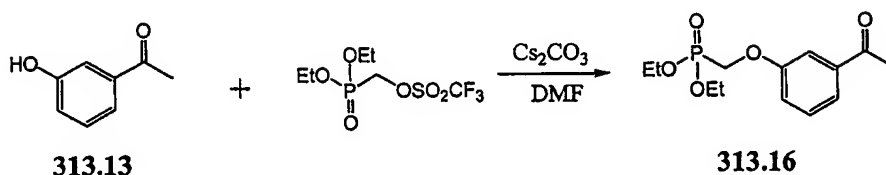
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Specific compounds of the invention can be prepared as follows:



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Preparation of 313.16



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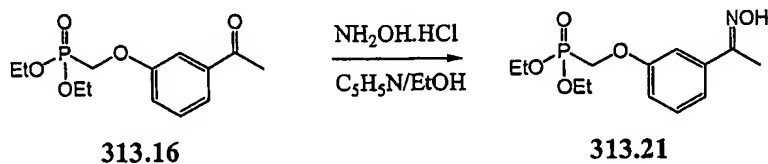
A reaction mixture of 3-hydroxyacetophenone (1.00g, 7.32mmol) trifluoromethanesulfonic anhydride (2.46g, 8.05 mmol) and cesium carbonate (2.86g, 8.79 mmol) in DMF (50mL) was stirred overnight at room temperature. The reaction mixture was diluted with water (100 mL) and the product was

15 extracted with ethyl acetate (2x100 mL), washed with water and brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with ethyl acetate/hexane (2:3), to yield the product (1.5 g, 72% yield).

MS m/z (MH)⁺ 287.

20

Preparation of Oxime 313.21

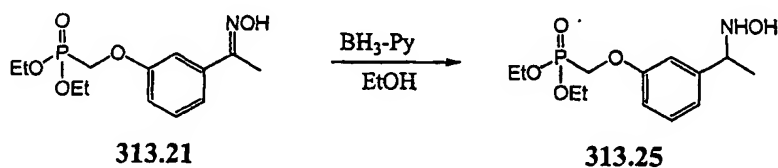


25

A mixture of 313.16 (0.5g, 1.75 mmol), hydroxylamine hydrochloride (0.145g, 2.09 mmol), pyridine (10 mL) and ethanol (10 mL) was stirred at room temperature for two days. The reaction mixture was concentrated to dryness, taken up in ether (20 mL) and washed with 3N HCl. The organic layer was dried
 5 over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting solid was purified chromatography on silica gel, eluting with CHCl₃:MeOH (98:2), to yield the desired product (0.3 g, 61%).

MS m/z (MH)⁺ 301.

10 Reduction of oxime 313.25



Oxime (313.21) (0.304 g, 1 mmol) was dissolved in ethanol (10 mL) and freshly-prepared BH₃-Py complex (1 mL) was added. The solution was stirred for 10 minutes at room temperature, whereupon 6 N HCl (1.8 mL) was added, dropwise. Further stirring was continued for 1 hour at room temperature. The reaction mixture was then brought to pH 8-9 by addition of 2N NaOH. The
 20 product was extracted with ethyl acetate (2x50 mL), dried over anhydrous sodium sulfate and concentrated to yield a viscous liquid (0.32 g) which contained some residual pyridine but was suitable for use in the next step.
 MS m/z (MH)⁺ 304.

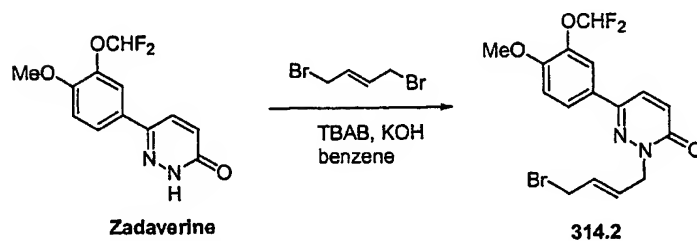
25 Synthesis of N -hydroxy urea (313.26)



To a solution of **313.21** (0.3 g, 1 mmol) in 1,4-dioxane (5 mL) and THF (5 mL) was added trimethylsilyl isocyanate (0.16 mL, 1.2 mmol). The reaction mixture was heated at 90 °C for 1 hour, cooled to room temperature and poured into a ice-cooled saturated solution of ammonium chloride. The product was
 5 extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with CHCl₃-MeOH, (96:4) to give the desired product (0.14 g, 40%). MS *m/z* (MH)⁺ 347. ¹H NMR (CDCl₃) δ 1.30-1.38 (m, 6H, 2-CH₃) 1.52-1.55 (d, 3H, CH₃, 4.1-4.37 (m, 6H, -CH₂-CH₂, OCH₂-P) 5.27-5.49 (m, 3H, -CH-, NH₂) 6.81-7.27 (m, 4H, C₆H₄) 8.13 (1H, N-OH). HPLC Purity 82
 10 % (sphereclone 5 μL H₂O: MeCN, 20 minute linear gradient from 10-90% MeCN, 1.0 mL/min). ³¹P NMR (CD₃OD) δ 21.69-22.12, m.

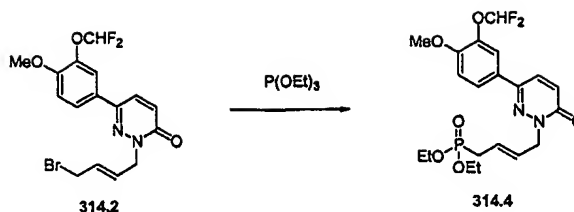
Example 314: Preparation of Representative Zardaverine Compounds of the Invention.
 15

Specific compounds of the invention can be prepared as follows:



Preparation of 314.2.

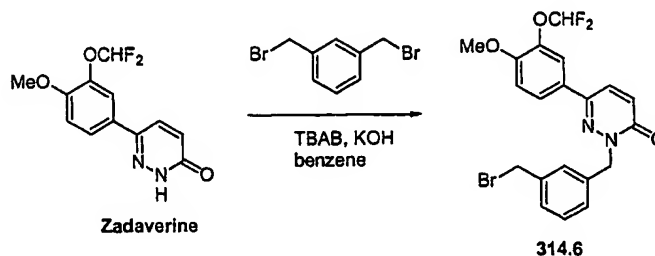
20 A mixture of 50 mg Zardaverine (0.186 mmol), 120 mg 1,4-dibromo-2-butene (0.56 mmol), 10.5 mg (0.187 mmol) KOH and 6.5 mg (0.02 mmol) TBAB in 1 mL benzene was stirred vigorously for 6 hrs. The suspension became two phases with a clear organic upper layer. TLC indicated the total consumption of the starting material and the formation of one new compound.
 25 The mixture was mounted directly on a silica gel column (1:1 hexanes/ethyl acetate) and 65 mg of the title compound was isolated as a white solid (87% yield). ESI-MS *m/z* 401 (MH)⁺. IR 1666 (C=O) cm⁻¹.



Preparation of 314.4

5 A solution of 65 mg 314.2 (0.125 mmol) and 0.22 mL (1.25 mmol) triethyl phosphite in 1 mL toluene was heated at reflux for 2 hrs. TLC indicated the total consumption of the starting material and the formation of one new compound. The mixture was mounted directly on a silica gel column (2% MeOH in ethyl acetate) and 65 mg of the title compound was isolated as a clear
 10 liquid (87% yield).

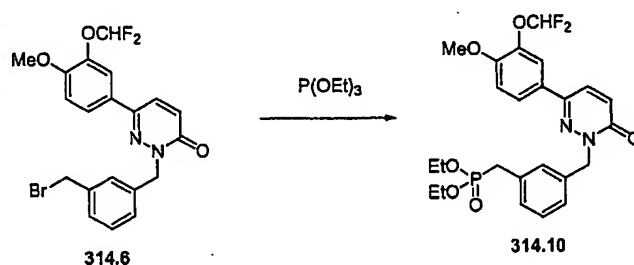
HPLC purity 100% (Sphereclone 5 μL , H_2O : MeCN, 20 min linear gradient from 10-90% MeCN, 1.0 mL/min). ESI-MS m/z 459 (MH)⁺. ¹H NMR (300 MHz, CDCl_3) δ 7.65 (d, J = 9.6 Hz, 1 H), 7.45 (d, J = 1.8 Hz, 1 H), 7.29-7.21 (m, 2 H), 7.03 (d, J = 9.6 Hz, 1 H), 6.61 (t, J = 74.8 Hz, 1 H), 5.98-5.72 (m, 2 H), 4.84 (t, J = 5.2 Hz, 2 H), 4.07 (quintet, J = 7.2 Hz, 4 H), 3.97 (s, 3 H), 2.62
 15 (dd, J = 21.4, 6.5 Hz, 2 H), 1.26 (t, J = 7.0 Hz, 6 H). ³¹P NMR (120 MHz, CDCl_3) δ 27.14 (m).



20 Preparation of 314.6

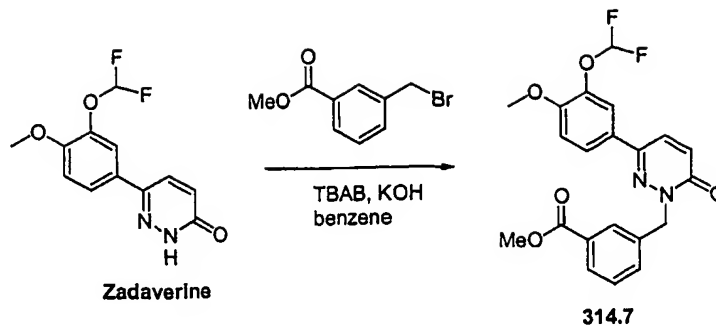
A mixture of 50 mg Zadaverine (0.186 mmol), 120 mg m-xylene dibromide (0.56 mmol), 10.5 mg (0.187 mmol) KOH and 6.5 mg (0.02 mmol)

TBAB in 1 mL benzene was stirred vigorously for 7.5 hrs. The suspension became two phases with a clear organic upper layer. TLC indicated the total consumption of the starting material and the formation of one new compound. The mixture was mounted directly on a silica gel column (1:1 hexanes/ethyl acetate) and 64 mg of the title compound was isolated as a white solid (77% yield). ESI-MS m/z 451 (MH)⁺.



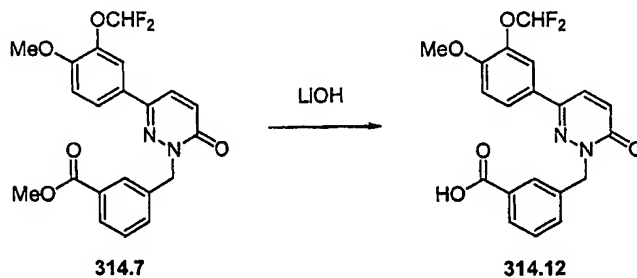
10 Preparation of 314.10

A solution of 64 mg 314.6 (0.142 mmol) and 0.22 mL (1.25 mmol) triethyl phosphite in 1 mL toluene was heated to reflux for 2 hrs. TLC indicated the total consumption of the starting material and the formation of one new compound. The mixture was mounted directly on a silica gel column (2% MeOH in ethyl acetate) and 70 mg of the title compound was isolated as a white solid (97% yield). HPLC purity >98% (Sphereclone 5 μ L, H₂O : MeCN, 20 min linear gradient from 10-90% MeCN, 1.0 mL/min). ESI-MS m/z 509 (MH)⁺. ¹H NMR (300 MHz, CDCl₃) δ 7.64 (d, J = 9.7 Hz, 1 H), 7.43 (d, J = 1.8 Hz, 1 H), 7.4-7.20 (m, 6 H), 7.02 (d, J = 9.7 Hz, 1 H), 6.60 (t, J = 74.9 Hz, 1 H), 5.39 (s, 2 H), 4.02-3.16 (m, 4 H), 3.96 (s, 3 H), 3.13 (d, J = 21.6 Hz, 2 H), 1.18 (t, J = 7.1 Hz, 6 H). ³¹P NMR (120 MHz, CDCl₃) δ 26.68 (m).



Preparation of 314.7

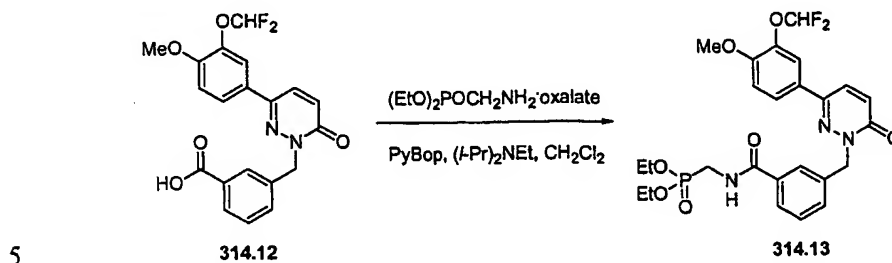
A mixture of 38 mg Zadaverine (0.142 mmol), 128 mg methyl 3-(bromomethyl)benzoate (0.56 mmol), 10.5 mg (0.187 mmol) KOH and 6.5 mg (0.02 mmol) TBAB in 1 mL benzene was stirred vigorously for 7.5 hrs. The suspension became two phases with a clear organic upper layer. TLC indicated the total consumption of the starting material and the formation of one new compound. The mixture was mounted directly on a silica gel column (1:1 hexanes/ethyl acetate) and 55 mg of the title compound was isolated as a white solid (94% yield). ESI-MS m/z 417 (MH)⁺.



Preparation of 314.12

A mixture of 55 mg Zadaverine (0.132 mmol), 55 mg LiOH·H₂O (1.3 mmol), 2 mL MeOH, 1 mL THF and 0.3 mL water was stirred vigorously at room temperature overnight. TLC indicated the total consumption of the starting material and the formation of one new compound. The solvent was evaporated under reduced pressure. The residue was diluted with CH₂Cl₂, acidified with 1 N

HCl, and extracted with CH_2Cl_2 . The organic phase was combined, dried and concentrated to give 49 mg of white solid (92% yield), which was used without further purification. ESI-MS m/z 403 $(\text{MH})^+$.



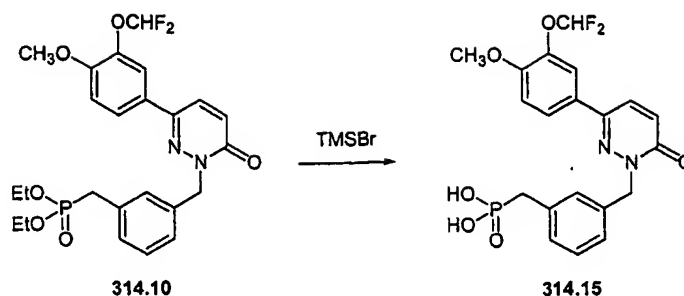
Preparation of 314.13

To a solution of 49 mg 314.12 (0.122 mmol) in 0.5 mL CH_2Cl_2 was added 76 mg PyBop (0.146 mmol) at 0°C , followed by 0.063 mL (*i*-Pr) $_2\text{NEt}$ (0.366 mmol). The mixture was stirred at room temperature for 2 hr until TLC indicated the total consumption of the starting material. The mixture was mounted directly on a silica gel column (45:1 ethyl acetate : methanol) and 45 mg of the title compound was isolated as a yellow solid (67% yield). HPLC purity >99% (Sphereclone 5 μL , H_2O : MeCN, 20 min linear gradient from 10-90% MeCN, 1.0 mL/min). ESI-MS m/z 552 $(\text{MH})^+$. ^1H NMR (300 MHz, CDCl_3) δ 7.92 (s, 1 H), 7.65 (d, $J = 9.8$ Hz, 1 H), 7.75-7.59 (m, 2 H), 7.48-7.38 (m, 2 H), 7.32-7.29 (m, 2 H), 7.03 (d, $J = 9.7$ Hz, 1 H), 6.60 (s, br, 1 H), 6.59 (t, $J = 74.8$ Hz, 1 H), 5.44 (s, 2 H), 4.20-4.10 (m, 4 H), 3.95 (s, 3 H), 3.89 (dd, $J = 12.1, 5.8$ Hz, 2 H), 1.31 (t, $J = 7.1$ Hz, 6 H). ^{31}P NMR (120 MHz, CDCl_3) δ 23.21 (m).

10

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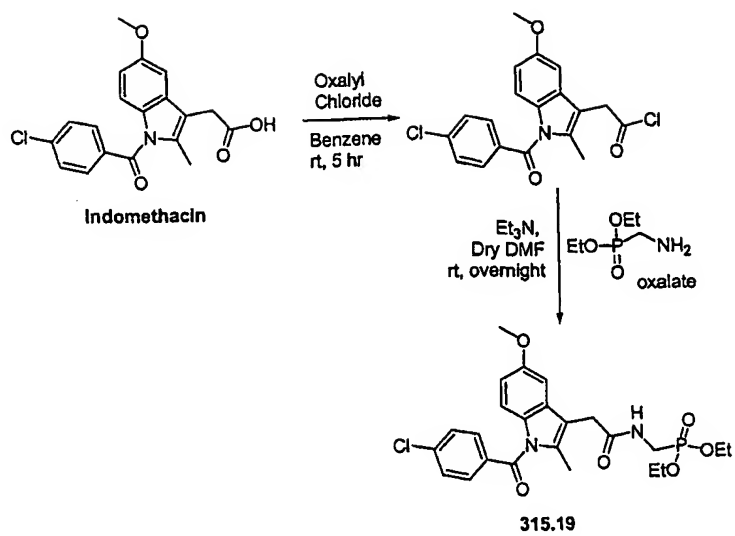


Preparation of 314.15

To 30 mg 314.10 (0.066 mmol) in 1.7 mL acetonitrile was added 0.3 mL TMSBr at 0 °C, and the solution was stirred at room temperature overnight. TLC indicated the total consumption of the starting material. The mixture was cooled to 0 °C before 1 mL MeOH was added, and the mixture was stirred at room temperature for 30 min. The solvent was then removed under vacuum. A sample of 5 mg of the red residue (total 30 mg) was cooled to 0 °C, 0.5 mL and 1 N NaOH was added, followed by 0.5 mL water. The mixture was stirred vigorously and then extracted with 1 mL ether 3 times. The aqueous phase was acidified to ca. pH 1 with concentrated HCl, and extracted with 2 mL portions of EtOAc 5 times. The combined EtOAc extracts were concentrated to furnish 3 mg of the title compound as a yellow solid (68 % yield). HPLC purity >95% (Sphereclone 5 μ L, H₂O : MeCN, 20 min linear gradient from 10-90% MeCN, 1.0 mL/min). ESI-MS m/z 453 (MH)⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.09 (d, J = 9.0 Hz, 1 H), 7.59-6.87 (m, 9 H), 5.31 (s, 2 H), 3.90 (s, 3 H), 2.96 (d, J = 22.1 Hz, 2 H).

Example 315: Preparation of Representative Indomethacin Compounds of the Invention.

Specific compounds of the invention can be prepared as follows.



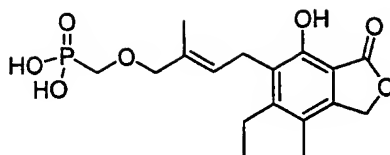
Synthesis of 315.19

Step 1: Indomethacin (500 mg, 1.40 mmol) was dissolved in dry benzene (5 mL) under an argon atmosphere, and oxalyl chloride (183 μ L, 2.10 mmol) was added, followed by 1 drop of dry DMF. The reaction mixture was stirred at room temperature for 24 hrs and concentrated to dryness. The residue was co-evaporated with dry benzene (5 mL) to remove traces of oxalyl chloride. The solid obtained (556 mg) was dried under vacuum for 4 hrs at room temperature and carried over to next step without purification.

Step 2: Diethyl(aminomethyl)phosphonate oxalate (381 mg, 1.48 mmol) was dissolved in 5 mL of dry DMF under argon atmosphere. Triethylamine (413 μ L, 2.96 mmol) was added, and the reaction mixture was stirred for 15 min at room temperature. The crude acid chloride (556 mg, 1.48 mmol) as a solution in 3 mL of dry DMF was added dropwise to the reaction mixture. After completion of the addition the reaction was stirred for 24 hrs at room temperature. TLC (CHCl_3 : MeOH, 95 : 5) showed complete consumption of starting material. Deionized water (10 mL) was added and the mixture was extracted with ethylacetate (2x15 mL). The ethyl acetate extracts were combined and washed with 1N HCl (5 mL) followed by deionized water (10 mL), and dried over Na_2SO_4 . Concentration gave a syrup that on purification by preparative-TLC (4 plates, 20x20 cm, 2000 microns, solvent: CHCl_3 : MeOH, 95 : 5) gave gummy solid. The gummy solid was crystallized from diethyl ether (3 mL) to give a solid (294 mg, 42% yield). HPLC: 99.5% pure (Sphereclone 5 μ L, H_2O : MeCN, 20 min linear from 10-90% MeCN, 1.0 mL/min). ESI-MS m/z 507 $[\text{M}+\text{H}]^+$. ^1H NMR (300 MHz, CDCl_3): δ 7.71-7.67 (2H, m, ArH), 7.51-7.48 (2H, m, ArH), 6.91-6.86 (2H, m, ArH), 6.72-6.68 (1H, dd, J = 8.9 Hz, 2.3 Hz, ArH), 5.82 (1H, br s, NH), 4.08-3.99 (4H, m, OCH_2), 3.83 (3H, s, OCH_3), 3.69-3.63 (4H, m, CH_2), 2.39 (3H, s, CH_3), 1.25-1.20 (6H, t, J = 7.0 Hz, CH_3). ^{31}P NMR (CDCl_3 , H_3PO_4 as external reference): δ 22.75

Example 316: Preparation of an Additional Representative Mycophenolate Compound of the Invention.

A specific compound of the invention can be prepared as follows.

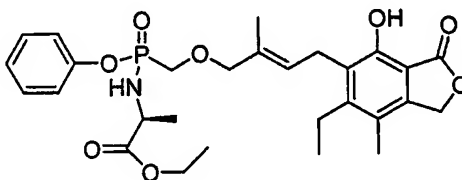


5 **[4-(6-Ethyl-4-hydroxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phosphonic acid**

This product was prepared using methods similar to those described herein, *e.g.*, in Examples 251 and 276. MS (negative mode): 369.3 [$M^+ - 1$].

10 **Example 317: Preparation of an Additional Representative Mycophenolate Compound of the Invention.**

A specific compound of the invention can be prepared as follows.



15 **2-[[4-(6-Ethyl-4-hydroxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enyloxymethyl]-phenoxy-phosphinoylamino}-propionic acid ethyl ester**

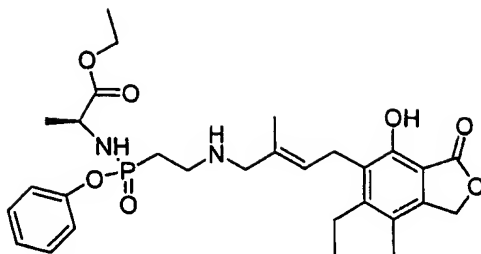
Using methods similar to those described herein, *e.g.*, in Example 261, the desired product was prepared, starting from Example 316. MS (positive mode): 546.3 [$M^+ + 1$] & 568.3 [$M^+ + Na$].

20

Example 318: Preparation of an Additional Representative Mycophenolate Compound of the Invention.

A specific compound of the invention can be prepared as follows:

25

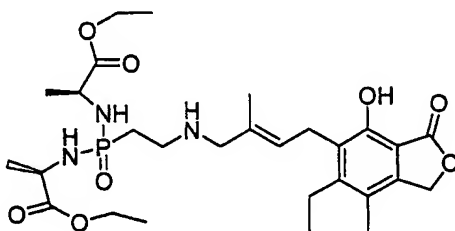


2-({2-[4-(6-Ethyl-4-hydroxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enylamino]-ethyl}-phenoxy-phosphinoylamino)-propionic acid ethyl ester

This product was prepared using methods analogous to those described herein, *e.g.*, in Examples 268 and 316, using 2-[(2-amino-ethyl)-phenoxy-phosphinoylamino]-propionic acid ethyl ester in the reductive amination step. MS (positive mode): 559.4 [$M^+ + 1$] & 581.3 [$M^+ + Na$].

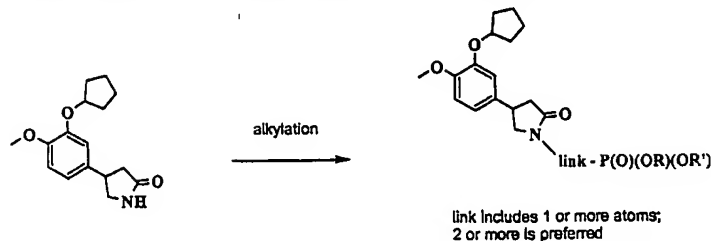
Example 319: Preparation of an Additional Representative Mycophenolate Compound of the Invention.

A specific compound of the invention can be prepared as follows:

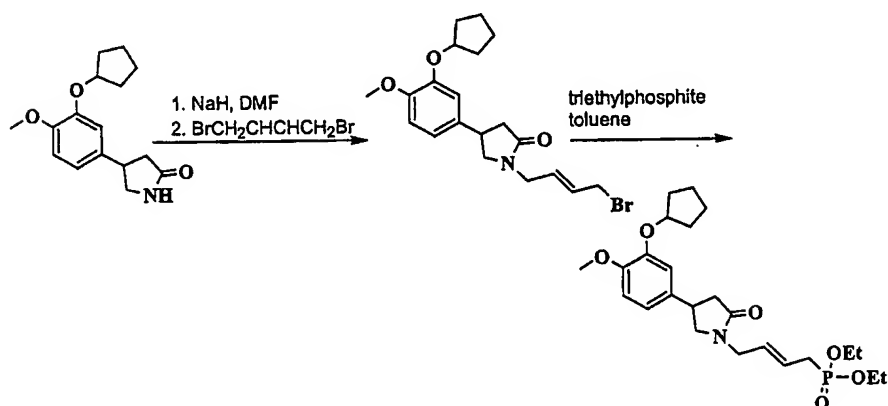


2-((1-Ethoxycarbonyl-ethylamino)-{2-[4-(6-ethyl-4-hydroxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-2-methyl-but-2-enylamino]-ethyl}-phosphinoylamino)-propionic acid ethyl ester

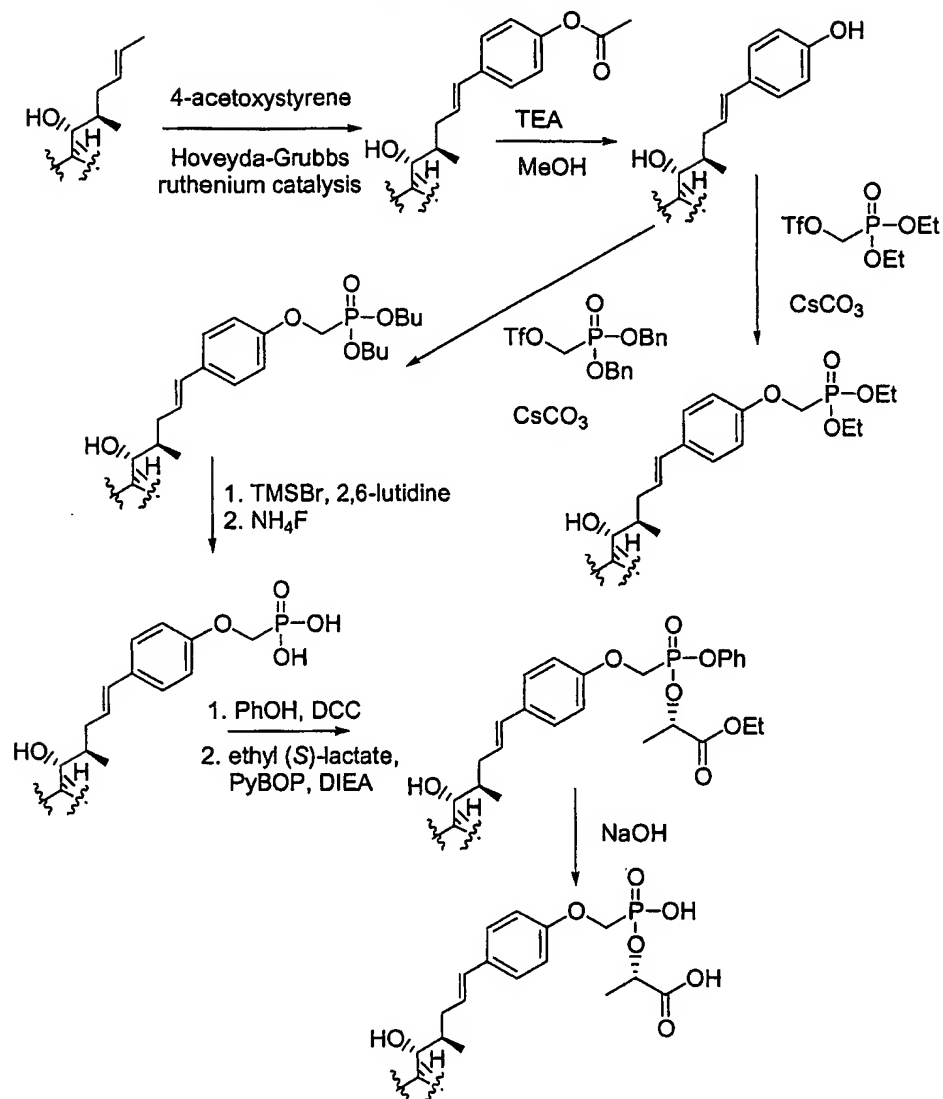
This product was prepared by methods analogous to those described herein, *e.g.*, in Example 318, using 2-[(2-aminoethyl)-(1-ethoxycarbonyl-ethylamino)-phosphinoylamino]-propionic acid ethyl ester in the reductive amination step. MS (positive mode): 582.4 [$M^+ + 1$] & 604.3 [$M^+ + Na$].

Example 320 Synthesis of Representative Compounds of the Invention

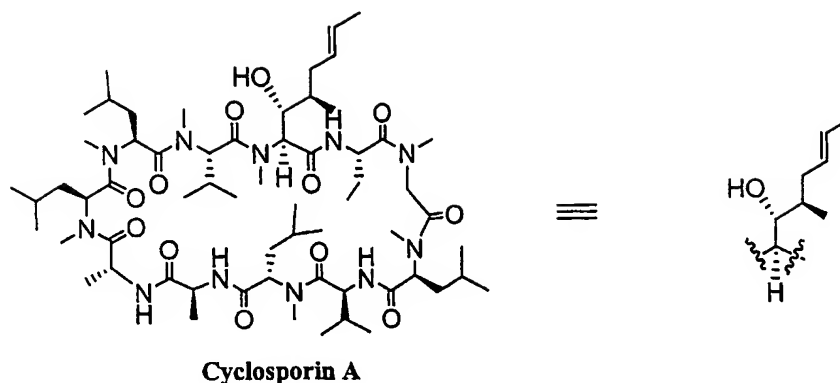
Representative compounds of the invention can be prepared as illustrated above. For example, a specific compound of the invention can be prepared as follows.



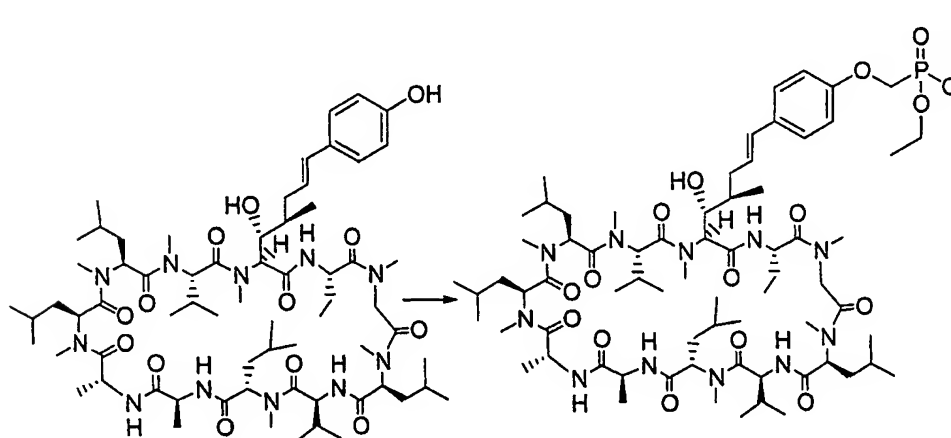
Rolipram can be treated in a solvent such as dimethylformamide or tetrahydrofuran with a base such as sodium hydride. When bubbling ceases, *E*-1,4-dibromobutene is added in excess. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated product is isolated by chromatography. The allylic bromide is then heated with triethylphosphite in a solvent such as toluene to generate the diethyl ester of the desired phosphonic acid.

Examples 321-325

The synthetic sequence used in Examples 321-325 for preparing representative compounds of the invention is illustrated above. In the above illustration the substructure on the right below represents Cyclosporin A.



Example 321 Synthesis of *cyclo*-[[*(2S, 3R, 4R, 6E)*-7-(4-(diethoxyphosphoryl-methoxy)phenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl]

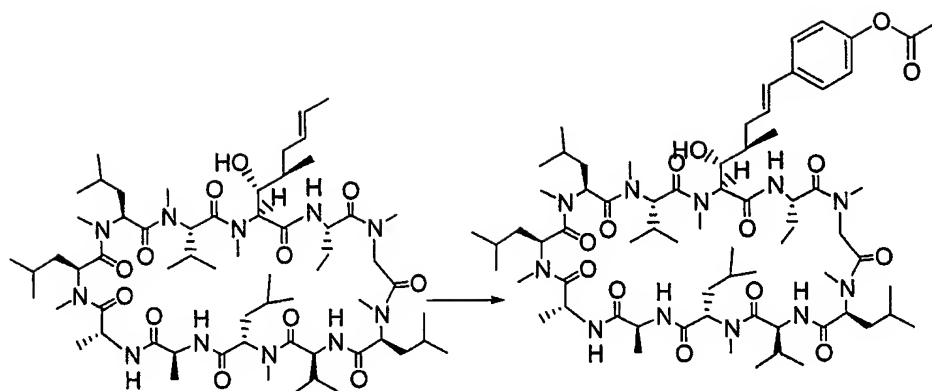


To a mixture of *cyclo*-[[*(2S, 3R, 4R, 6E)*-7-(4-hydroxyphenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl] (113 mg, 0.088 mmol) and cesium carbonate (33 mg, 0.1 mmol) in DMF (1 mL) was added trifluoromethanesulfonic acid

diethoxyphosphorylmethyl ester (60 mg, 0.2 mmol). The mixture was stirred at room temperature for 16 hours. The reaction was quenched with 2 % aqueous lithium chloride and the mixture was extracted with ethyl acetate. The ethyl acetate extract was concentrated *in vacuo*. The residue was purified by silica gel column chromatography to provide the desired product (310 mg, 83%) contaminated with the unreacted starting materials, which was further purified by RP HPLC using a Phenomenex Synergi 5 μ Hydro RP 80A column (50 x 21.2 mm) with eluents of H₂O - CH₃CN. The fractions containing the desired product were pooled and concentrated to dryness (62 mg, 49 %). MS (*m/z*) 1431.0 [M+H]⁺, 1428.7 [M-H]⁻; ³¹P (121.4 MHz, CDCl₃) δ 19.5.

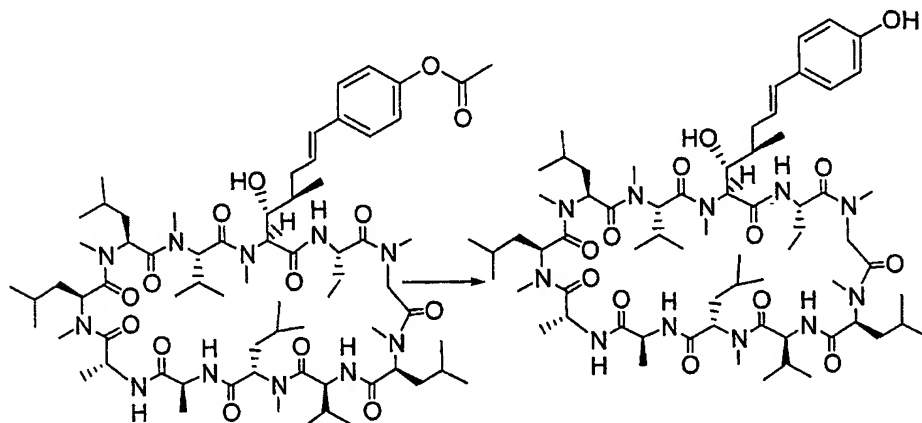
The intermediate compound *cyclo*-[[*(2S, 3R, 4R, 6E)*-7-(4-hydroxyphenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl] was prepared as follows.

a. *cyclo*-[[*(2S, 3R, 4R, 6E)*-7-(4-Acetoxyphenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl]



A mixture of cyclosporin A (360 mg, 0.3 mmol), 4-acetoxystyrene (730 mg, 4.5 mmol) and (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidene)dichloro(*O*-isopropoxyphenylmethylene)ruthenium (Hoveyda-Grubbs catalyst, 20 mg, 0.032 mmol) in dichloromethane (1 mL) was purged with nitrogen and stirred under reflux for 16 hours. After cooling, the reaction mixture was purified by silica gel column chromatography using MeOH - CH₂Cl₂ to provide the product as a solid (395 mg, 99 %). MS (*m/z*) 1322.9 [M+H]⁺, 1344.9 [M+Na]⁺; HPLC retention time 3.3 min. (relative to 4.1 min. of cyclosporin A; Phenomenex Synergi 4 micron hydro-RP 80A 50x4.6 mm; solvents, 35 % water and 65% acetonitrile; flow rate 2 mL/min.; column temperature 60 °C).

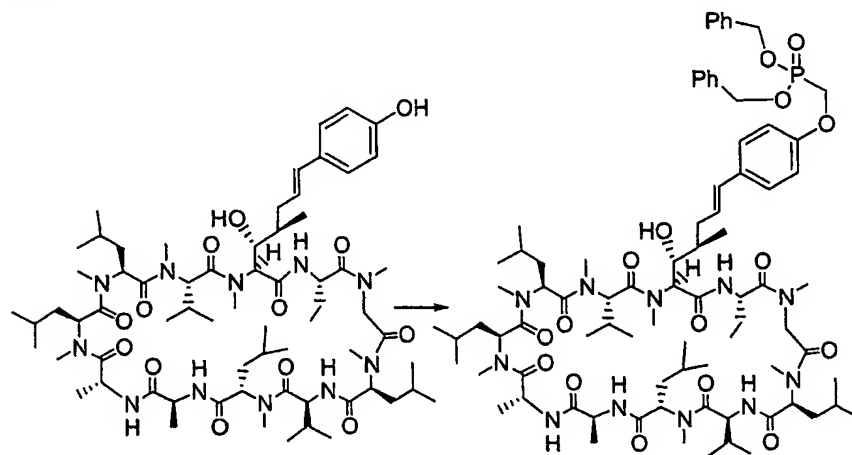
b. *cyclo*-[[*(2S, 3R, 4R, 6E)*-7-(4-Hydroxyphenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]



A solution of *cyclo*-[[*(2S, 3R, 4R, 6E)*-7-(4-acetoxystyryl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl] (385 mg, 0.29 mmol) and triethylamine (1 mL) in MeOH (10 mL) was stirred at ambient temperature for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography using MeOH - CH₂Cl₂ to provide the desired product (310 mg, 83%). MS (*m/z*) 1280.9 [M+H]⁺, 1278.8 [M-H]⁻; HPLC retention time 1.6 min. (relative to 4.0 min. of cyclosporin A; Phenomenex Synergi 4 micron hydro-RP 80A 50x4.6 mm; solvents, 35 % water and 65% acetonitrile; flow rate 2 mL/min.; column temperature 60 °C).

Example 322 Synthesis of *cyclo*-[[*(2S, 3R, 4R, 6E)*-7-(4-(dibenzoyloxy-phosphoryl-methoxy)phenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-

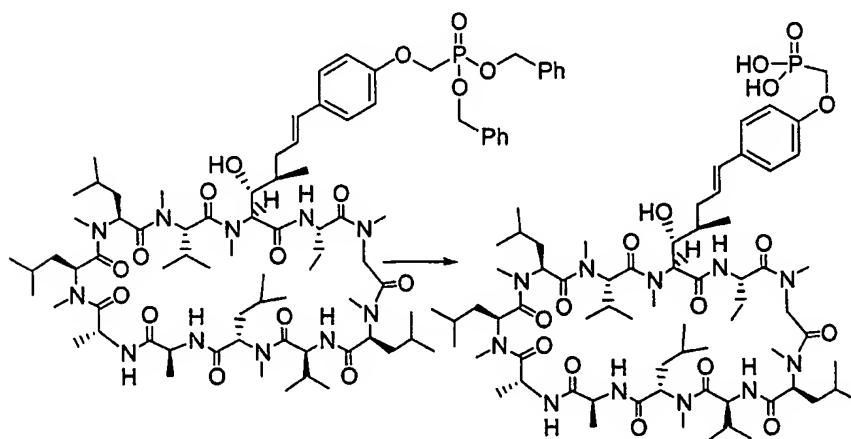
leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]



To a mixture of *cyclo*-[[*(2S, 3R, 4R, 6E)*-7-(4-hydroxyphenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl] (300 mg, 0.234 mmol) and cesium carbonate (326 mg, 1 mmol) in DMF (2 mL) was added trifluoromethanesulfonic acid dibenzyloxyphosphorylmethyl ester (60 mg, 0.2 mmol). The mixture was stirred at room temperature for 16 hours. The reaction mixture was filtered through Acrodisc (13 mm syringe filter with 0.45 micron Nylon membrane) and purified by RP HPLC using a Phenomenex Synergi 5 μ Hydro RP 80A column (50 x 21.2 mm) with eluents of H₂O- CH₃CN. The fractions containing the desired product were pooled and concentrated to dryness, affording a white solid (115 mg, 32 %). MS (*m/z*) 1554.9 [M+H]⁺, 1552.7 [M-H]⁻; ³¹P (121.4 MHz, CDCl₃) δ 20.5.

Example 323 Synthesis of *cyclo*-[[*(2S, 3R, 4R, 6E)*-7-(4-(diethoxyphosphoryl)phenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-

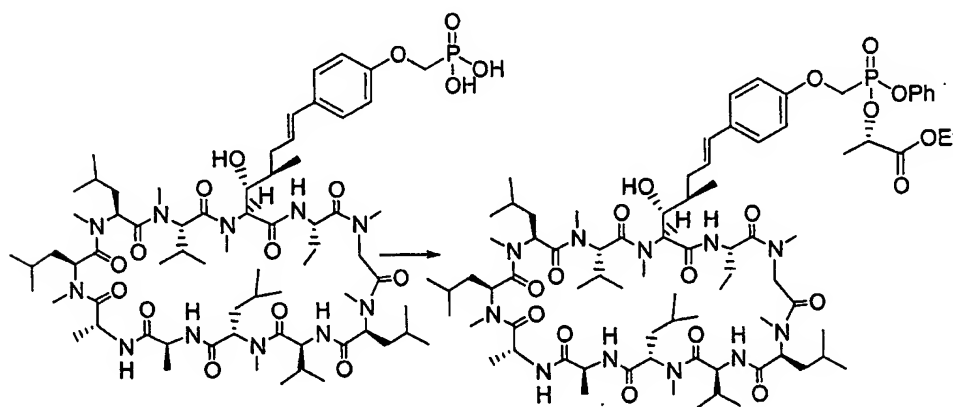
leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]



To a mixture of *cyclo*-[[[(2*S*, 3*R*, 4*R*, 6*E*)-7-(4-(dibenzoyloxyphosphoryl-methoxy)phenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl] (115 mg, 0.074 mmol) and 2,6-lutidine (40 μ L, 0.35 mmol) in dichloromethane (2 mL) was added trimethylsilyl bromide (50 μ L, 0.35 mmol). The mixture was stirred at room temperature for 2 hours. The reaction was quenched with methanol (1 mL) and the mixture was concentrated. The residue was treated with a solution of ammonium fluoride (0.5 M, 2 mL), stirred for 1 hour, concentrated, and partitioned between dichloromethane and 1 N HCl. The dichloromethane layer was concentrated and the crude product was purified by RP HPLC using a Phenomenex Synergi 5 μ Hydro RP 80A column (50 x 21.2 mm) with eluents of 0.1 % TFA H₂O - 0.1 % TFA CH₃CN. The fractions containing the desired product were pooled and concentrated to dryness, affording a hygroscopic solid (68 mg, 63 %). MS (*m/z*) 1374.9 [M+H]⁺, 1373.1 [M-H]⁻; HPLC retention time 0.3 min. (relative to 4.0 min. of cyclosporin A; Phenomenex Synergi 4 micron hydro-RP 80A 50x4.6 mm;

solvents, 35 % water and 65% acetonitrile; flow rate 2 mL/min.; column temperature 60 °C).

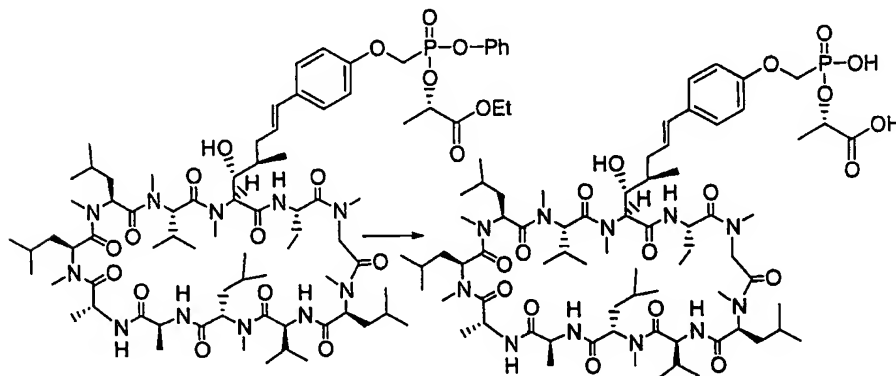
Example 324 Synthesis of *cyclo*-[[(2*S*, 3*R*, 4*R*, 6*E*)-7-(4-(1-(*S*)-ethoxycarbonylethoxy)phenoxyphosphoryl-methoxy)phenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl]



A mixture of *cyclo*-[[(2*S*, 3*R*, 4*R*, 6*E*)-7-(4-(dihydroxyphosphoryl)ethoxy)phenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl] (34 mg, 0.023 mmol), phenol (22 mg, 0.23 mmol), dicyclohexylcarbodiimide (47 mg, 0.23 mmol) and 4-(*N,N*-dimethylamino)pyridine (5.6 mg, 0.046 mmol) in DMF (2 mL) was stirred at 140 °C for 20 min. After cooling, the monophenyl monophosphonic acid product was purified by RP HPLC using a Phenomenex Synergi 5 μ Hydro RP 80A column (50 x 21.2 mm) with eluents of 0.1 % TFA H₂O- 0.1 % TFA CH₃CN. MS (*m/z*) 1450.9 [M+H]⁺, 1449.1 [M-H]⁻; ³¹P (121.4 MHz, CDCl₃) δ 14.9. This intermediate was mixed with ethyl (*S*)-(-)-lactate (40 mg, 0.34 mmol), PyBOP (80 mg, 0.15

mmol), diisopropylethylamine (45 μ L, 0.26 mmol) and DMF (1.7 mL). The resulting mixture was stirred at room temperature for 2 hours. After removal of insoluble impurities, the crude product was purified by RP HPLC using a Phenomenex Synergi 5 μ Hydro RP 80A column (50 x 21.2 mm) with eluents of 0.1 % TFA H₂O - 0.1 % TFA CH₃CN. The desired fractions were pooled and partitioned between acetonitrile and saturated aqueous sodium bicarbonate. The organic layer was concentrated to afford the product as a solid (12 mg, 34 %). MS (m/z) 1573.1 [M+Na]⁺, 1548.8 [M-H]⁻; ³¹P (121.4 MHz, CDCl₃) δ 15.3 and 17.4.

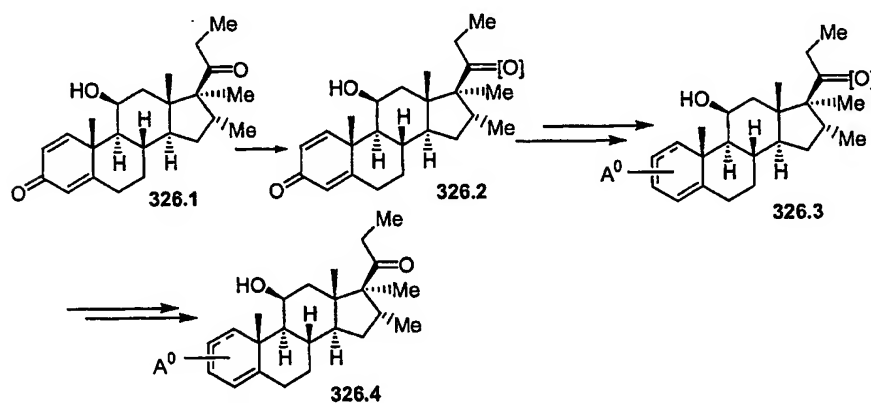
Example 325 Synthesis of *cyclo*-[[[(2*S*, 3*R*, 4*R*, 6*E*)-7-(4-(1-(*S*)-hydroxycarbonylethoxy)hydroxyphosphorylmethoxy)phenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl]



To a solution of *cyclo*-[[[(2*S*, 3*R*, 4*R*, 6*E*)-7-(4-(1-(*S*)-ethoxycarbonylethoxy)phenoxyphosphorylmethoxy)phenyl)-4-methyl-3-hydroxy-2-(methylamino)-6-heptenoyl]-L-2-aminobutyryl-sarcosyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl] (5 mg, 3.2 μ mol) in a mixed solvent of water and acetonitrile (0.5 mL and 4.5 mL) was added 1 N NaOH (40 μ L). The solutions was stirred at room temperature for 2

hours. The resulting reaction mixture was concentrated and purified by RP HPLC using a Phenomenex Synergi 5 μ Hydro RP 80A column (50 x 21.2 mm) with eluents of 0.1 % TFA H₂O - 0.1 % TFA CH₃CN. The desired fraction was concentrated to dryness affording the product as a solid (1.5 mg, 32 %). MS (m/z) 1446.9 [M+H]⁺, 1444.9 [M-H]⁻; HPLC retention time 0.2 min. (relative to 4.0 min. of cyclosporin A; Phenomenex Synergi 4 micron hydro-RP 80A 50x4.6 mm; solvents, 35 % water and 65% acetonitrile; flow rate 2 mL/min.; column temperature 60 °C).

Example 326 Synthesis of Representative compounds of the Invention



A protection-deprotection sequence in which the 20-ketone group of Rimexolone is protected to afford the derivative 326.2 is illustrated above. The ketone is protected, for example, by conversion to the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, 77:1904(1955). Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in *J. Chem. Soc., Chem. Comm.*, 1351(1987).

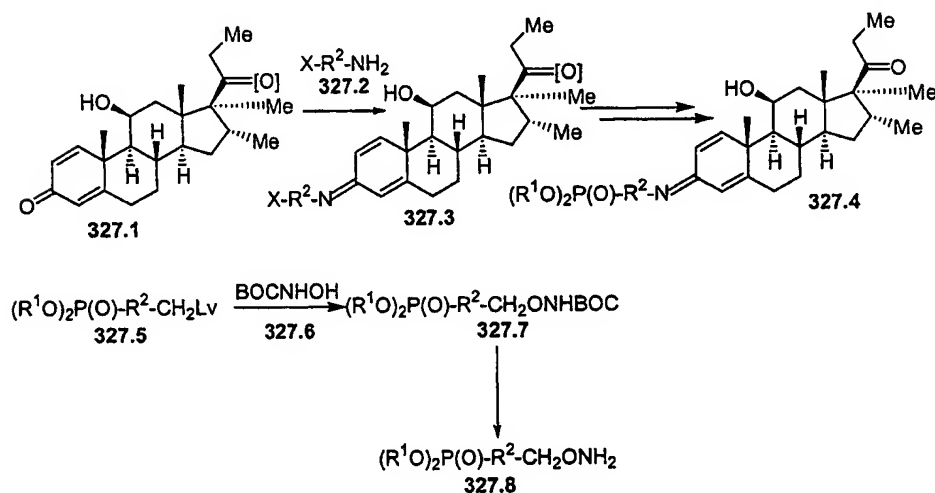
Alternatively, the 20-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone 326.1 with N,N-dimethylhydrazine in ethanol-acetic acid, as described in *Org. Syn.*, 50:102(1970). The group is removed by treatment with sodium acetate

and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.*, 101, 5841(1979).

Alternatively, the 20-ketone is protected as the diethylamine adduct. In this procedure, the substrate **326.1** is reacted with titanium tetrakis(diethylamide), as described in *J. Chem. Soc., Chem. Comm.*, 406 (1983), to afford the adduct. The ketone is deprotected by reaction with water in an aqueous organic solvent.

The protected compound **326.2** is then converted into the phosphonate-containing analog **326.3**, using the procedures described below, and the protecting group or groups are then removed, as described above, to give the phosphonate **326.4**.

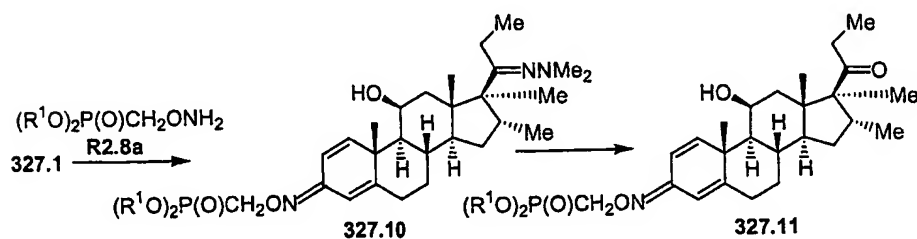
Example 327 Synthesis of Representative Compounds of the Invention



The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the ketone-protected derivative **327.1** is reacted with an amine or hydroxylamine **327.2**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional

group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime **327.3**. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, 86:133(1978). and in *J. Mass. Spectrom.*, 30:497(1995). The protecting group is then removed to afford the 20-keto phosphonate product **327.4**.

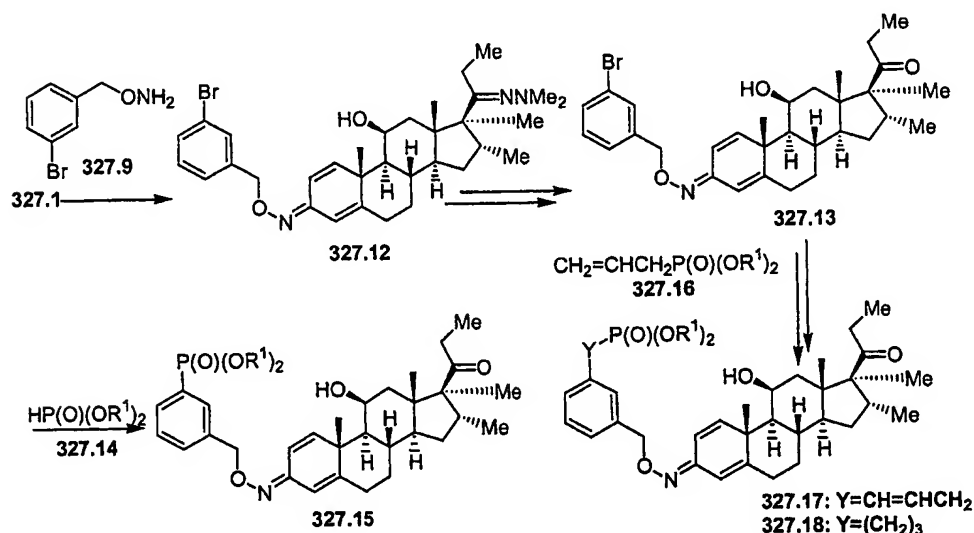
The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated above. In this procedure, a phosphonate **327.5**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine **327.6** (Aldrich) to produce the ether **327.7**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether **327.8**. The above procedure is also employed for the preparation of substituted hydroxylamines which are precursors to phosphonates.



The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate **327.1**, in which the 20-ketone is protected as the dimethyl hydrazone derivative, is

reacted with a dialkyl phosphonomethyl hydroxylamine **327.8a**, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (Tet. Lett., 1986, 27, 1477) and BOC-hydroxylamine, to afford the oxime **327.10**. Deprotection affords the 20-keto phosphonate **327.11**. The oxime forming reaction is typically performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether **327.8a**, different oxime ethers **327.2**, the corresponding products **327.4** are obtained.

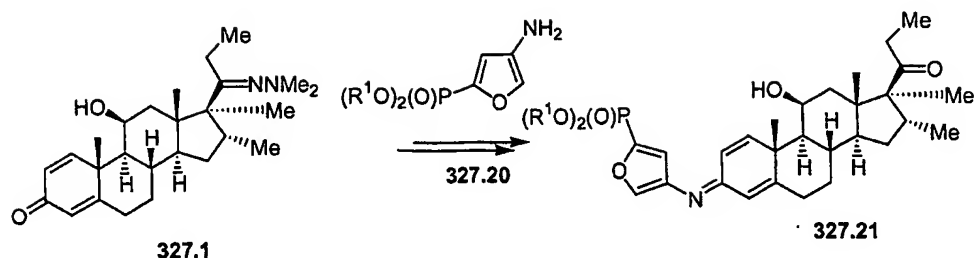


The preparation of compounds in which the phosphonate group is attached by means of a benzyloxy oxime group is illustrated above. In this procedure, the dienone **327.1**, in which the 20-ketone is protected as the dimethyl hydrazone, is reacted, as described above, with O-(3-bromobenzyl)hydroxylamine **327.9**, prepared as described above from 3-bromobenzyl bromide and BOC-protected hydroxylamine **327.6**, to give the oxime **327.12**. The protecting group is then removed to yield the 20-keto product **327.13**. The latter product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **327.14** to afford the

phosphonate **327.15**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, 35:1371(1992). The reaction is performed at ca. 100°C in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

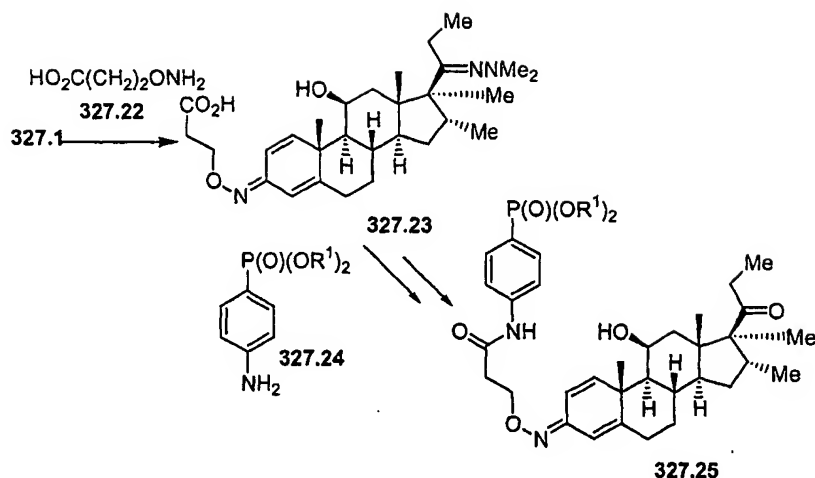
Alternatively, the bromo compound **327.13** is coupled with a dialkyl propenylphosphonate **327.16** (Aldrich) to afford the phosphonate **327.17**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, 503ff(Plenum, 2001) and in *Acc. Chem. Res.*, 12:146(1979). The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)-palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product **327.17** is reduced, for example by reaction with diimide, to produce the saturated analog **327.18**. The reduction of olefinic bonds is described in R. C. Larock, *Comprehensive Organic Transformations*, 6ff(VCH, 1989). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromobenzyl reagent **327.9**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds **327.15**, **327.17** and **327.18** are obtained.



The preparation of phosphonates in which the phosphonate is attached by means of a 4-furylimino group is illustrated above. In this procedure, the substrate 327.1, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with a dialkyl 4-amino-2-furyl phosphonate 327.20, prepared by the palladium catalyzed coupling reaction, as described above, between 4-amino-2-bromofuran (*Tet.*, 43:3295(1987)) and a dialkyl phosphite, to give, after deprotection, the imine product 327.21. The imine forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions.

Using the above procedures, but employing, in place of the 4-aminofuryl phosphonate 327.20 different amino-substituted aryl or heteroaryl phosphonates, products analogous to 327.21 are obtained.



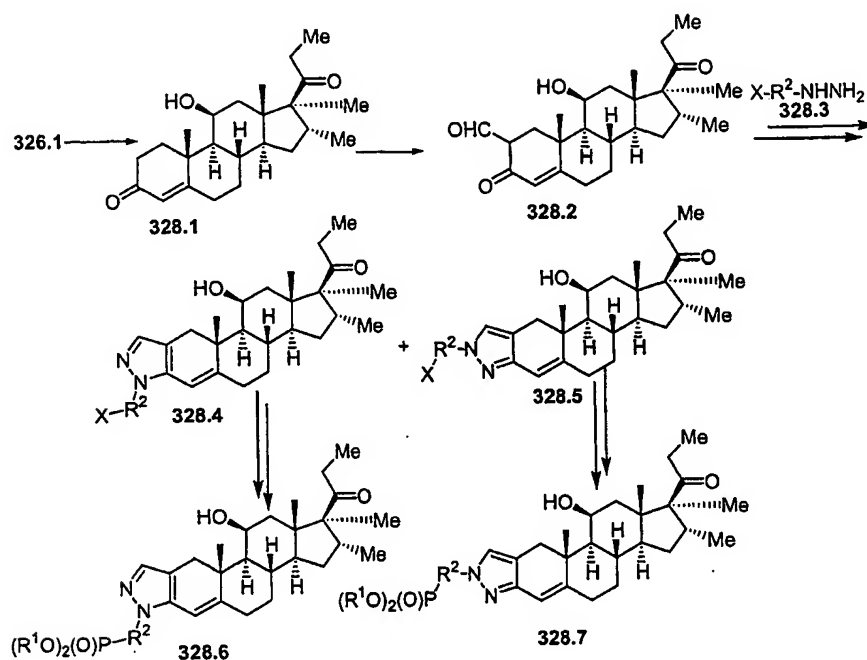
The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and an amide linkage is illustrated above. In this procedure, the dienone 327.1, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with 2-carboxyethyl hydroxylamine 327.22 (*J. Med. Chem.*, 33:1423(1990)) to yield the oxime 327.23. The reaction of steroidal 1,4-dien-3-ones with hydroxylamines is described in *J. Steroid Bioch.*, 7:795(1976); the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product 327.23 is then coupled with a dialkyl 4-aminophenyl phosphonate 327.24 (Epsilon) and dicyclohexyl carbodiimide, to yield, after deprotection, the amide oxime 327.25. The preparation of amides from carboxylic acids and derivatives is described, for example, in S.R.Sandler and W. Karo, *Organic Functional Group Preparations*, 274(Academic Press, 1968), and R. C. Larock, *Comprehensive Organic Transformations*, 972ff (VCH, 1989). The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

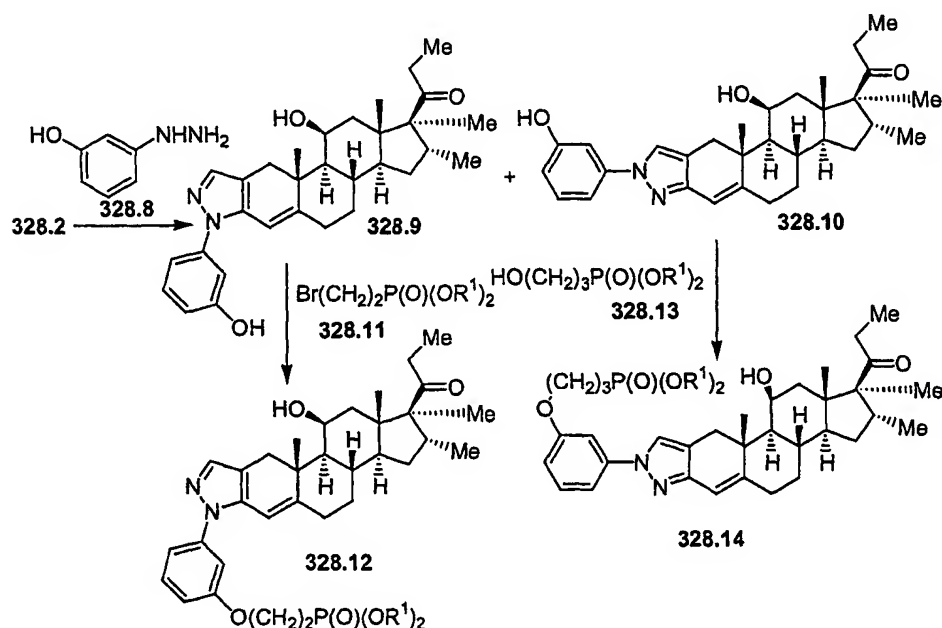
Using the above procedures, but employing, in place of the carboxy-substituted hydroxylamine **327.22**, different carboxy-substituted hydroxylamines, and/or different amino-substituted phosphonates, the products analogous to **327.25** are obtained.

Example 328 Synthesis of Representative compounds of the Invention



The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and/or a variable carbon chain is illustrated above. In this procedure, the dienone 326.1 is reduced to afford the 1,2-dihydro product 328.1. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, 44:602(2001). The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, 86:1520(1964), to afford the 2-formyl product 328.2. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine 328.3, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The

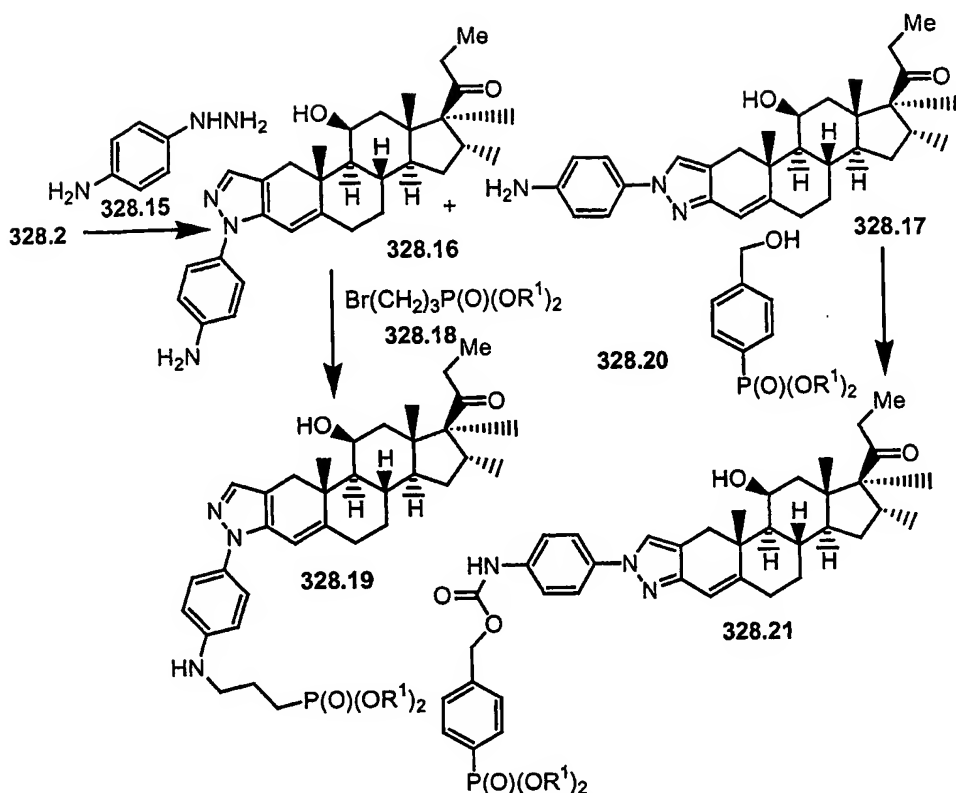
reaction yields the isomeric 2'- and 1'-aryl pyrazoles **328.4** and **328.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, 86:1520(1964). The pyrazoles **328.4** and **328.5** are then transformed into the phosphonates **328.6** and **328.7**. Optionally, the reduction and formylation reactions are performed on the substrate **326.2** in which the 20-ketone is protected as the cyclic ethylene ketal.



The preparation of phosphonates in which the phosphonate is attached by means of a phenyl ring and an alkoxy group is illustrated above. In this procedure, the ketoaldehyde **328.2** is reacted, as described above, with 3-hydroxyphenylhydrazine **328.8** (JP 03011081) to give the pyrazoles **328.9** and **328.10**. The 2'-substituted isomer **328.9** is then reacted in dimethylformamide solution at 70° with one molar equivalent of a dialkyl 2-bromoethyl phosphonate **328.11**(Aldrich) and potassium carbonate, to give the ethoxy phosphonate **328.12**.

The isomeric pyrazole 328.10 is reacted in a Mitsunobu with one molar equivalent of a dialkyl 3-hydroxypropyl phosphonate 328.13 (*Zh. Obshchei. Khim.*, 44:1834(1974)) to yield the phosphonate 328.14. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in R. C. Larock, *Comprehensive Organic Transformations*, 448(VCH, 1989), and in F.A. Carey and R. J. Sundberg, *Advanced Organic Chemistry, Part B*, 153-4(Plenum, 2001) and in *Org. React.*, 42:335(1992). The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, 42:335-656(1992).

Using the above procedures, but employing different hydroxy-substituted hydrazines, and/or different bromo or hydroxy-substituted phosphonates, the products analogous to 328.12 and 328.14 are obtained.

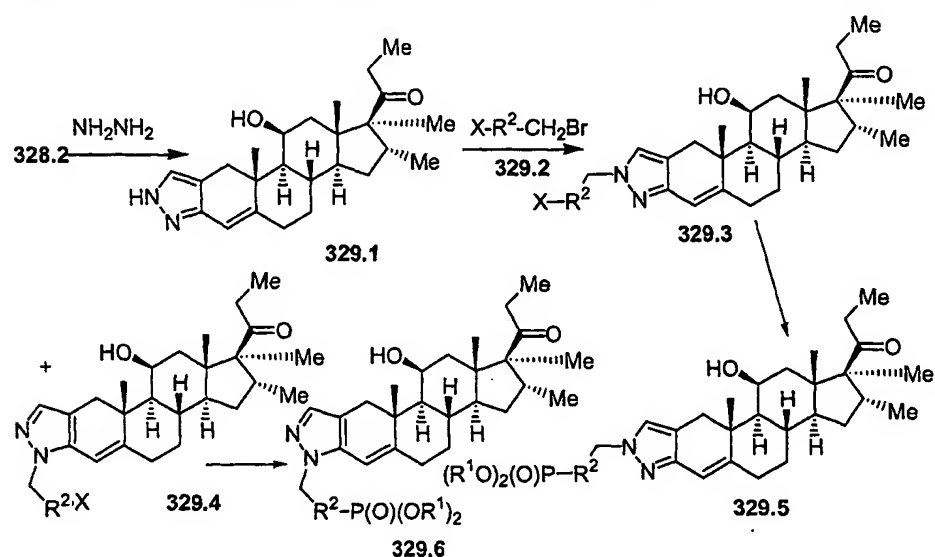


The preparation of the phosphonates in which the phosphonate group is attached by means of an amino or a carbamate group and an aromatic ring is illustrated above. In this procedure, the ketoaldehyde 328.2 is reacted, as described above, with 4-aminophenyl hydrazine 328.15 (Syn. Comm., 4:57(1974)) to produce the pyrazoles 328.16 and 328.17. The 2'-substituted isomer 328.16 is then reacted in dimethylformamide solution at 70° with one molar equivalent of a dialkyl 3-bromopropyl phosphonate 328.18 (J. Amer. Chem. Soc., 122:1554(2000)) and cesium carbonate, to give the amine phosphonate 328.19.

Alternatively, the 1'-substituted pyrazole 328.22 is coupled with a dialkyl 4-hydroxymethylphenyl phosphonate 328.20 (US 5569664) and carbonyl diimidazole to prepare the carbamate phosphonate 328.21. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p 416ff, and in Organic Functional Group

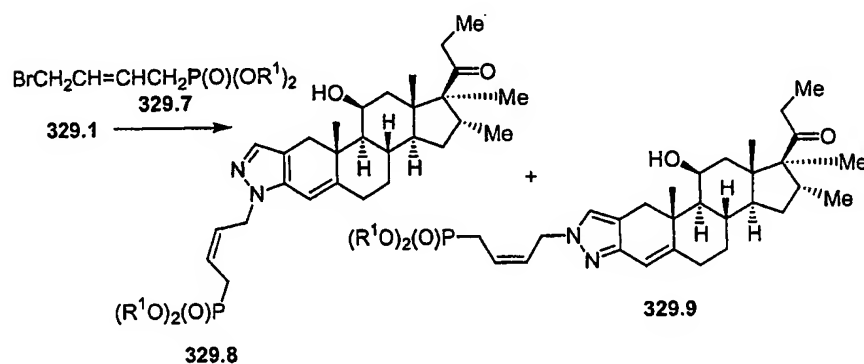
Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff. In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate. Using the above procedures, but employing, in place of the aminophenyl hydrazine **328.15**, different amino-substituted hydrazines, and/or different dialkyl bromo or hydroxy-substituted phosphonates, the products analogous to the compounds **328.19** and **328.21** are obtained.

Example 329 Synthesis of Representative compounds of the Invention



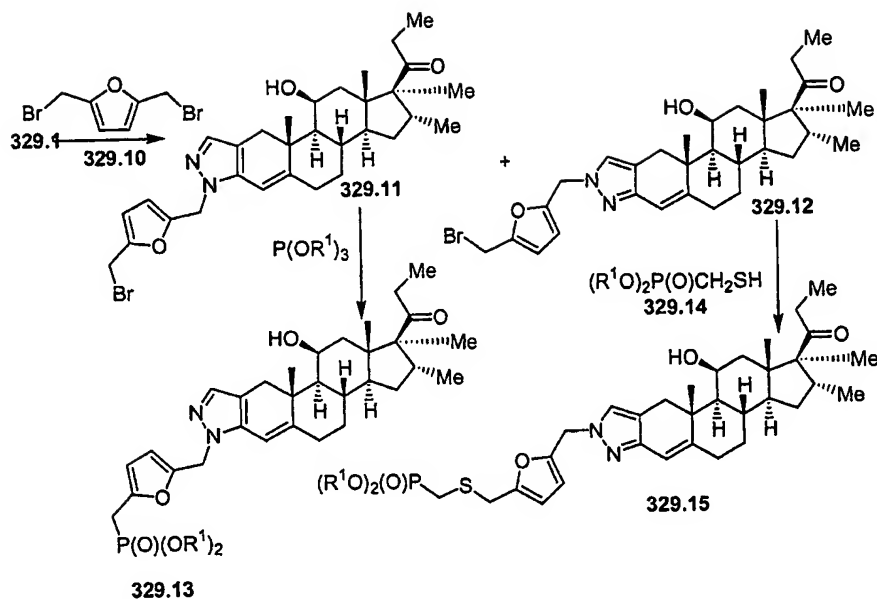
The phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde **328.2** is reacted with hydrazine to afford the pyrazole derivative **329.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, 1964, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound

329.2, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products **329.3** and **329.4**. The alkylation of substituted pyrazoles is described, for example, in *Heterocyclic Chemistry*, by T. L. Gilchrist, Longman, 1992, p. 309. The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products **329.3** and **329.4** are, except in cases where X is dialkylphosphono, converted into the phosphonates **329.5** and **329.6**, using the procedures described herein.



Representative compounds of the invention can be prepared as illustrated above. The pyrazole **329.1** is reacted in dimethylformamide solution at 70°C with one molar equivalent of a dialkyl 4-bromobutenyl phosphonate **329.7** (*J. Med. Chem.*, 1992, 35, 1371) and lithium hexamethyl disilazide, to give the pyrazoles **329.8** and **329.9**.

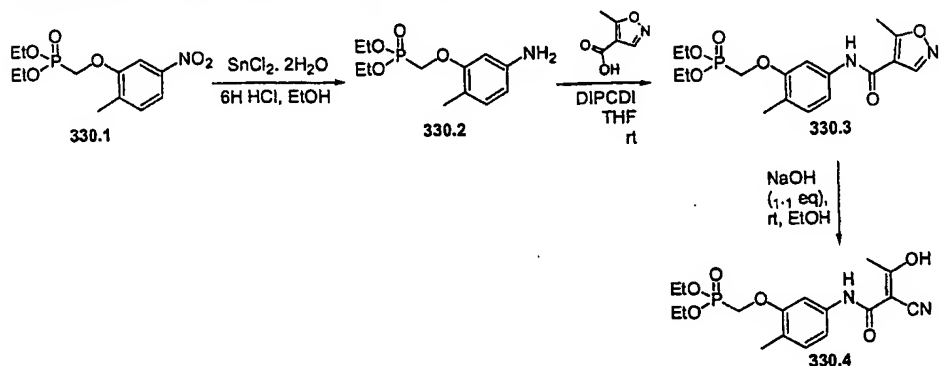
Using the above procedures, but employing different bromo-substituted phosphonates, the products analogous to **329.8** and **329.9** are obtained.



Representative compounds of the invention can be prepared as illustrated above. The pyrazole **329.1** is reacted in tetrahydrofuran solution with 2,5-bis(bromomethyl)furan **329.10** (*Tet.*, 1999, 55, 4709) and potassium hexamethyl disilazide, to give the alkylation products **329.11** and **329.12**. The 2'-substituted isomer **329.11** is then reacted, in a Arbuzov reaction, with a trialkyl phosphite to yield the phosphonate **329.13**. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, 1992, 115. In this procedure, in which a bromo substituent is converted into the corresponding phosphonate, the substrate is heated at from about 60° to about 160° with a five to fifty-fold molar excess of a trialkyl phosphite, to effect the transformation.

The 1'-substituted pyrazole **329.12** is reacted at ambient temperature in dimethylformamide solution with one molar equivalent of a dialkyl mercaptomethyl phosphonate **329.14** (*J. Med. Chem.*, 1985, 26, 1688) and cesium carbonate, to give the thioether phosphonate **329.15**.

Using the above procedures, but employing different dihalides, and/or different mercapto-substituted phosphonates, the products analogous to **329.13** and **329.15** are obtained.

Example 330 Synthesis of Representative Compounds of the Invention

A representative compound of the invention **330.4** can be prepared as illustrated above and as described below.

Compound **303.3** (250 mg, 0.65 mmol) was dissolved in 10 mL of absolute ethanol (15 mL) under an argon atmosphere. Following the addition of NaOH (29 mg, 0.72 mmol), the reaction mixture was stirred overnight at room temperature. TLC (CHCl₃/MeOH, 9 : 1) showed completion of reaction. The reaction mixture was concentrated to a solid and dissolved in ethyl acetate (20 mL). The solution was washed with deionized water (2x10 mL) and dried over Na₂SO₄. Concentration gave a solid that was purified by silica gel column chromatography (CHCl₃/MeOH, 4 : 1), affording pure compound **330.4** as a solid (188 mg, 75%). ESI-MS *m/z* 383 [M+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.32 (1H, s, ArH), 6.96 (2H, s, ArH), 4.31 (2H, d, *J* = 9.9 Hz, OCH₂), 4.18-4.08 (4H, m, 2xOCH₂), 2.08 (3H, s, CH₃), 2.00 (3H, s, CH₃), 1.26 (6H, t, *J* = 7.0 Hz, CH₃). ³¹P NMR (121.7 MHz, DMSO-*d*₆/external H₃PO₄) δ □ppm 20.0-20.4 (m); HPLC: 93% pure (Sphereclone 5 μL, H₂O : MeCN, 20 min linear from 10-90% MeCN, 1.0 mL/min).

The intermediate compound **330.3** was prepared as follows.

- a. **Synthesis of Compound 330.1.** 2-Methyl-5-nitrophenol (2.00 g, 13.05 mmol) was dissolved in dry DMF (10 mL) under argon atmosphere and cooled to 0

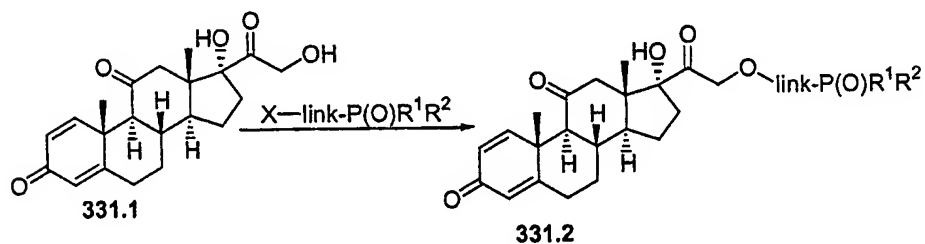
°C. Diethylphosphonomethyl-*O*-triflate (4.70 gm, 15.66 mmol) and cesium carbonate (6.38 gm, 19.58 mmol) were added sequentially. The reaction mixture was stirred at 0 °C for 4 hrs. TLC (cyclohexane/EtOAc, 1:1) showed completion of reaction. Deionized water (15 mL) was added and the mixture was extracted with EtOAc (2x50 mL). The organic layer was washed with 1N HCl (20 mL) followed by water (2x20 mL), dried over Na₂SO₄ and concentrated to a semi-solid. Purification by silica gel column chromatography (cyclohexane/EtOAc, 1 : 1) afforded pure compound 330.1 as an oil (3.86 g, 97%). ESI-MS *m/z* 304 [M+H]⁺.

b. **Synthesis of Compound 330.2.** Compound 330.1 (2.8 g, 9.24 mmol) was dissolved in 15 mL of absolute ethanol (15 mL) and 6N HCl (2 mL) under an argon atmosphere. Following the addition of SnCl₂ · 2H₂O (5.26 g, 27.72 mmol), the reaction mixture was stirred overnight at room temperature. TLC (CHCl₃/MeOH, 9 : 1) showed completion of reaction. The mixture was concentrated to a semi-solid and dissolved in ethyl acetate (30 mL). The ethyl acetate layer was washed with deionized water (10 mL) and satd. NaHCO₃ (10 mL) and dried over Na₂SO₄. Concentration gave a solid that was used without purification. ESI-MS *m/z* 274 [M+H]⁺.

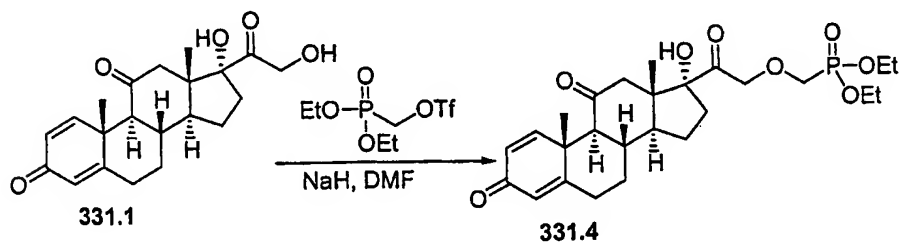
c. **Synthesis of Compound 330.3.** Crude compound K-105-48 (900 mg, 3.38 mmol) was dissolved in 15 mL of dry THF (15 mL) under an argon atmosphere. Following the addition of 5-methylisoxazole-4-carboxylic acid (381 mg, 3.00 mmol) and diisopropyl carbodiimide (511 µL, 3.30 mmol), the reaction mixture was stirred 6 h at room temperature. TLC (CHCl₃/MeOH, 9 : 1) showed completion of reaction. The reaction mixture was filtered and the filtrate concentrated to give a solid, which was dissolved in ethyl acetate (25 mL). The solution was washed with deionized water (2x10 mL) and dried over Na₂SO₄. Concentration gave a solid that was purified by silica gel column chromatography (CHCl₃/MeOH, 95 : 5) to afford pure compound 330.3 as light yellow solid (680 mg, 55%). ESI-MS *m/z* 383

$[M+H]^+$. ^1H NMR (300 MHz, CDCl_3): δ 7.11 (1H, s, ArH), 7.06 (2H, s, ArH), 4.29-4.20 (4H, m, OCH_2), 4.14 (2H, d, $J = 10.4$ Hz, OCH_2), 2.76 (3H, s, CH_3), 2.14 (3H, s, CH_3), 1.37 (6H, t, $J = 7.0$ Hz, CH_3). ^{31}P NMR (121.7 MHz, DMSO-d_6 /external H_3PO_4) δ ppm 19.7-20.0 (m); HPLC: 98 % pure (Sphereclone 5 μL , $\text{H}_2\text{O} : \text{MeCN}$, 20 min linear from 10-90% MeCN , 1.0 mL/min).

Example 331 Synthesis of Representative Prednisone Compounds of the Invention

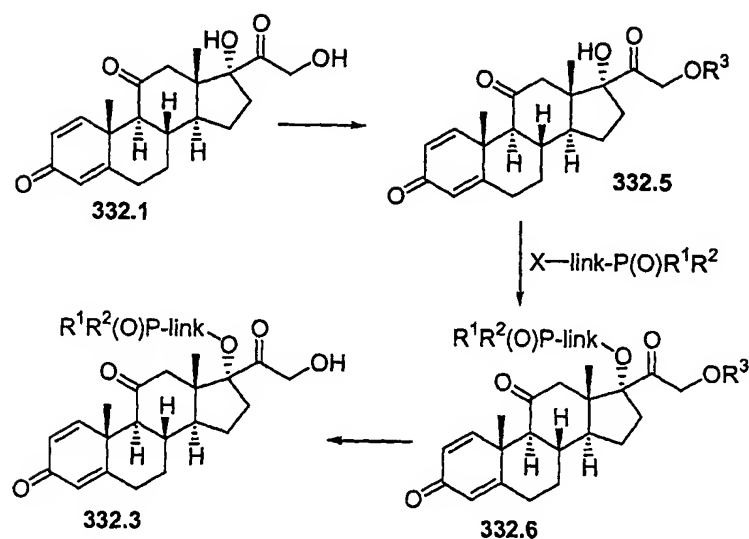


Representative compounds of the invention can be prepared as illustrated above. Derivatization at the C-21 hydroxy group is accomplished through alkylation of prednisone 331.1 with the appropriate phosphonate to provide compounds of the invention 331.2. A specific compound of the invention can be prepared as follows.

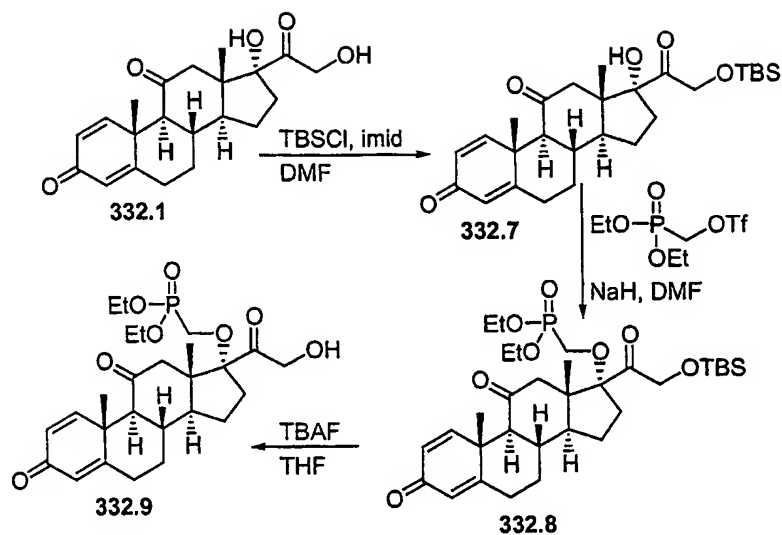


After sodium hydride extraction of the primary hydroxy proton in 331.1, diethyl phosphonate triflate is added to afford ether 331.4.

Example 332 Synthesis of Representative Prednisone Compounds of the Invention



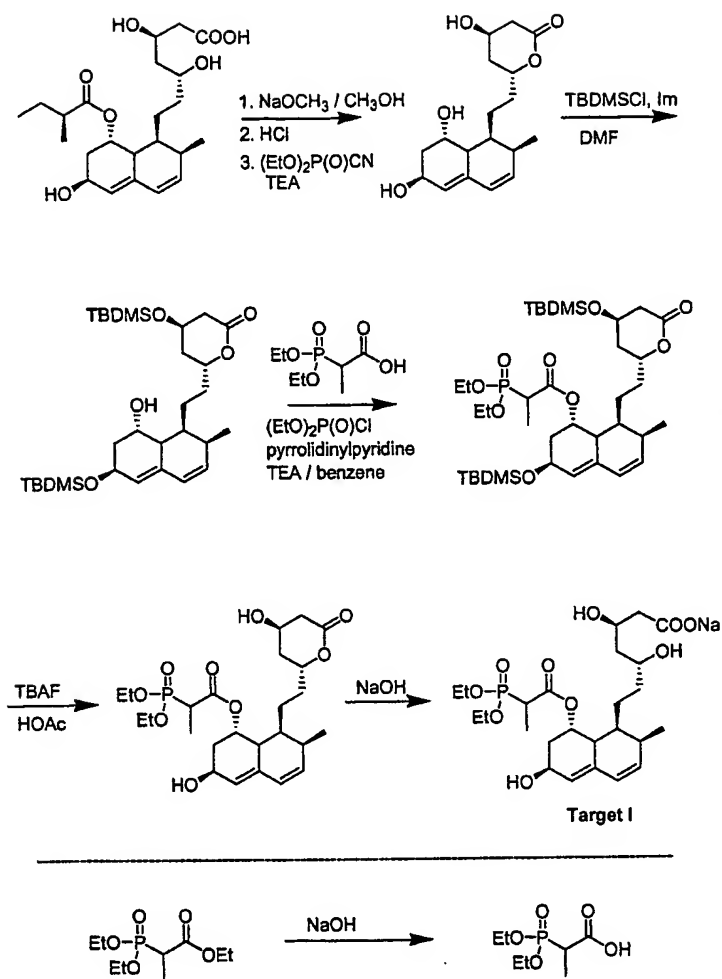
Representative compounds of the invention 332.3 can be prepared as illustrated above. Protection of prednisone 332.1 at the less hindered primary site furnishes alcohol 332.5, which is alkylated at the exposed hydroxy group with the appropriate phosphonate to provide 332.6. Removal of the protecting group completes the construction of analog 332.3. A specific compound can be prepared as follows.



Prednisone **332.1** is mono-protected as its TBS ether **332.7**. After alkylating with the diethyl phosphonate triflate, the resulting intermediate **332.8** is treated with TBAF to give the desired phosphonate **332.9**.

Example 333 Synthesis of Representative Compounds of the Invention

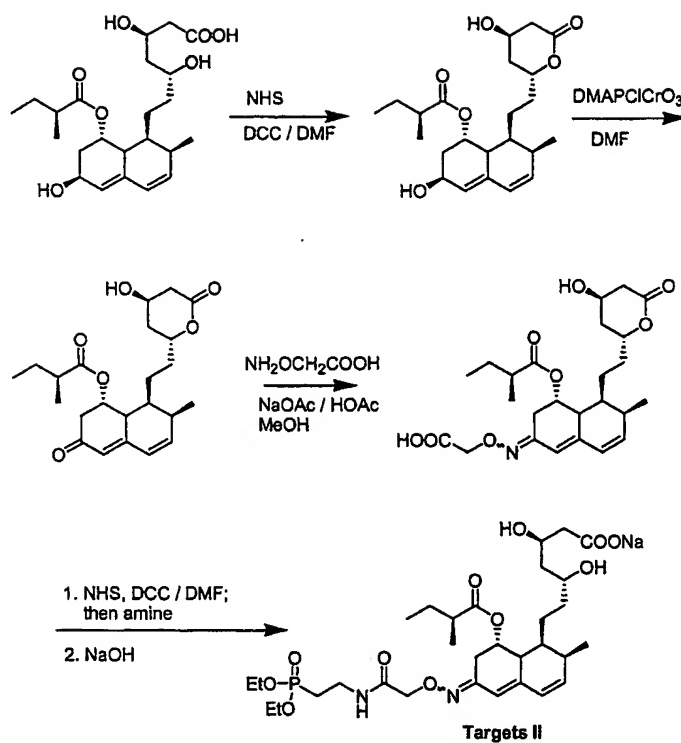
A synthetic scheme for the preparation of compounds of the invention is as follows:



The de-acylation and re-acylation of pravastatin is disclosed in EP 0609058

A2.

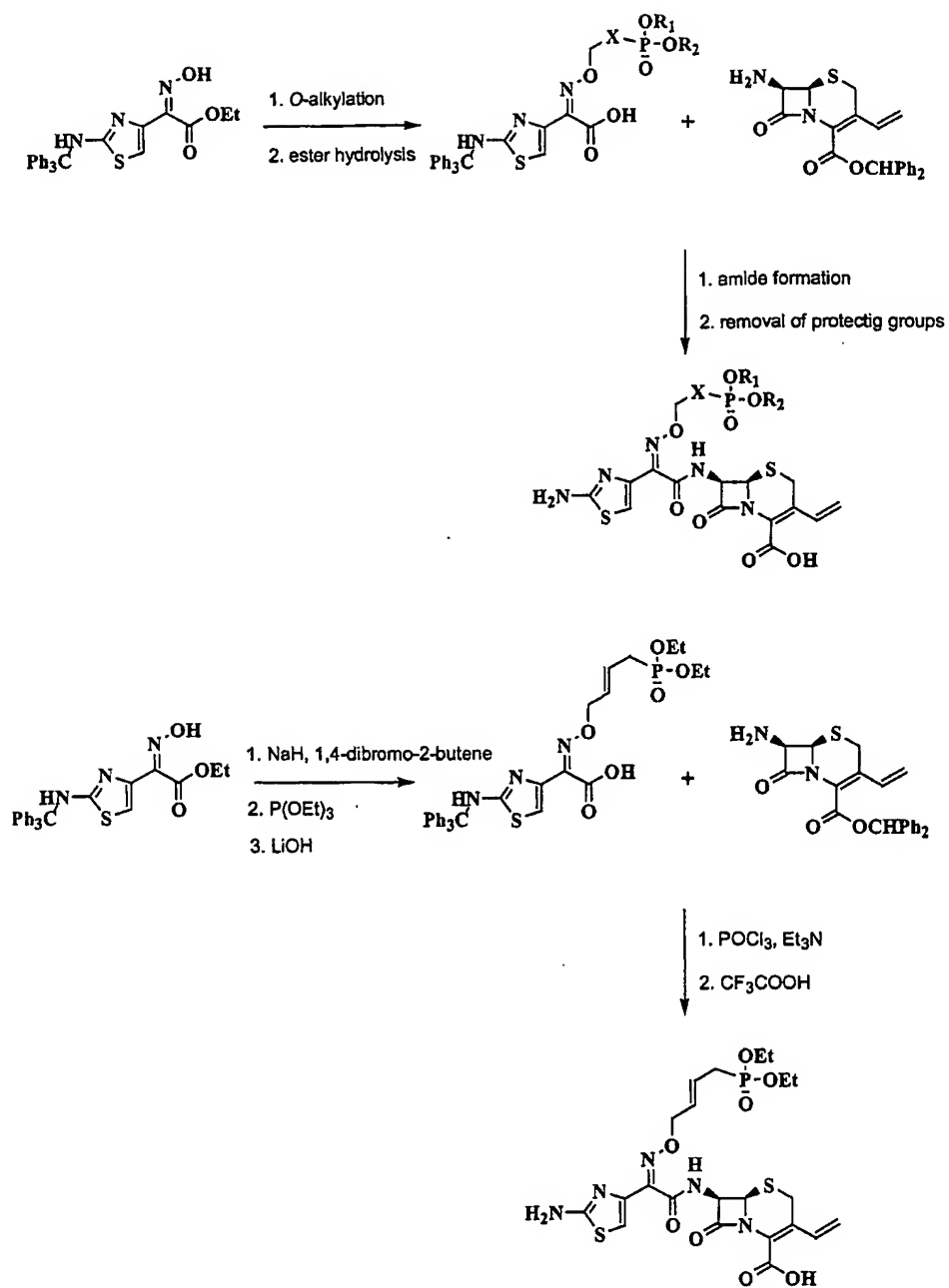
In addition, representative compounds of the invention may be prepared as follows:



The oxime formation is disclosed in Bioorg. Med. Chem., 3:1479 (1995).

Example 334 Synthesis of Representative Compounds of the Invention

Representative compounds of the invention can be made according to the general route outlined below.



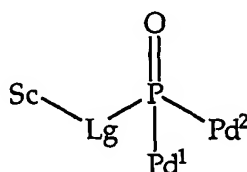
Hydroxyimino-[2-(tritylamino)-thiazol-4-yl]acetic acid ethyl ester
(commercially available) can be treated in a solvent such as dimethylformamide

(DMF) or tetrahydrofuran (THF) with a base such as sodium hydride. When bubbling ceases, 1,4-dibromo-2-butene is added in excess. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated product is isolated by chromatography. The allylic bromide is then heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions; see Engel, R., "Synthesis of Carbon-phosphorus Bonds," CRC press, (1988)) to generate [4-(diethoxyphosphoryl)-but-2-enyloxyimino]-[2-(tritylamino)-thiazol-4-yl]-acetic acid ethyl ester.

The ester is hydrolyzed to the acid, which is coupled with 7-amino-8-oxo-3-vinyl-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid benzhydryl ester (obtained as described in Tet. Lett., 35:9601 (1994)), following a procedure such as that reported in J. Antibiotic., 53:1045 (2000). The coupled product is then treated with trifluoroacetic acid to afford the desired phosphonate-containing analog.

Example 335

By way of example and not limitation, embodiments of the invention are named below in tabular format (Table 100). These embodiments are of the general formula "MBF":

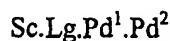


MBF

5

Each embodiment of MBF is depicted as a substituted nucleus (Sc). Sc is described in Tables 1.1 to 1.5 below. Sc is also described by any formula presented herein that bears at least one A⁰, wherein A⁰ is the point of covalent attachment of Sc to Lg. For those embodiments described in Table 100, Sc is a nucleus designated by a number and each substituent is designated in order by letter or number. Tables 1.1 to 1.5 are a schedule of nuclei used in forming the embodiments of Table 100. Each nucleus (Sc) is given a number designation from Tables 1.1 to 1.5, and this designation appears first in each embodiment name. Similarly, Tables 10.1 to 10.19 and 20.1 to 20.36 list the selected linking groups (Lg) and prodrug (Pd¹ and Pd²) substituents, again by letter or number designation, respectively. Accordingly, a compound of the formula MBF includes compounds having Sc groups based on compounds according to Table 100 below. In all cases, compounds of the formula MBF have groups Lg, Pd¹ and Pd² setforth in the Tables below.

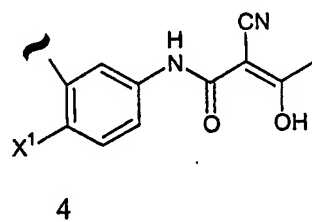
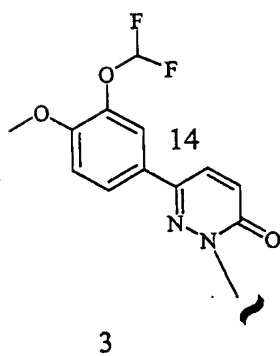
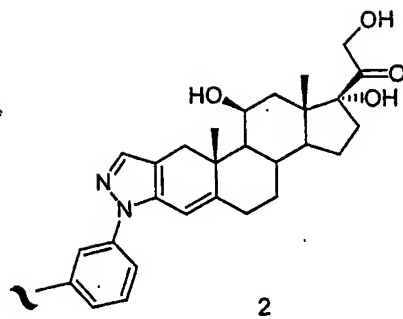
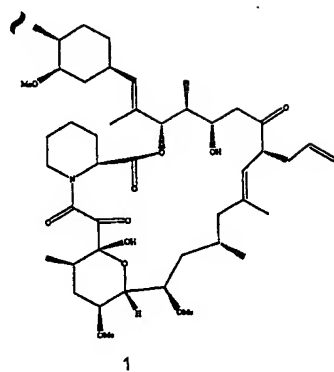
Accordingly, each named embodiment of Table 100 is depicted by a number designating the nucleus from Table 1.1-1.5, followed by a letter designating the linking group (Lg) from Table 10.1-10.19, and two numbers designating the two prodrug groups (Pd¹ and Pd²) from Table 20.1-20.36. In graphical tabular form, each embodiment of Table 100 appears as a name having the syntax:



~~PCT/US2004/013283~~

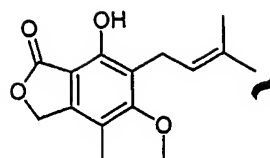
- Each Sc group is shown having a tilde ("~"). The tilde is the point of covalent attachment of Sc to Lg. Q¹ and Q² of the linking groups (Lg), it should be understood, do not represent groups or atoms but are simply connectivity designations. Q¹ is the site of the covalent bond to the nucleus (Sc) and Q² is the site of the covalent bond to the phosphorous atom of formula MBF. Each prodrug group (Pd¹ and Pd²) are covalently bonded to the phosphorous atom of MBF at the tilde symbol ("~") or the A⁰ symbol. Some embodiments of Tables 10.1-10.19 and 20.1-20.36 may be designated as a combination of letters and numbers (Table 10.1-10.19) or number and letter (Table 20.1-20.36). For example there are Table 10 entries for BJ1 and BJ2. In any event, entries of Table 10.1-10.19 always begin with a letter and those of Table 20.1-20.36 always begin with a number. When a nucleus (Sc) is shown enclosed within square brackets ("[]") and a covalent bond extends outside the brackets, the point of covalent attachment of Sc to Lg may be at any substitutable site on SC.
- Selection of the point of attachment is described herein. By way of example and not limitation, the point of attachment is selected from those depicted in the schemes and examples.

Table 1.1

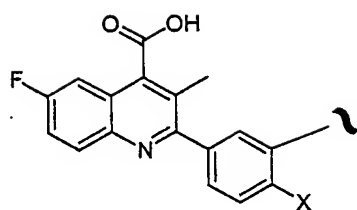


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Table 1.2

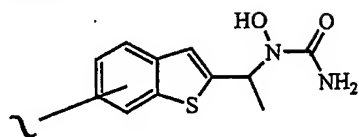


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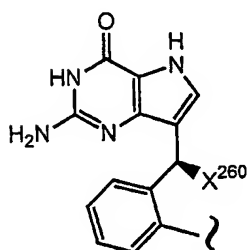


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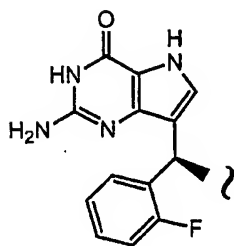
Table 1-3

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9

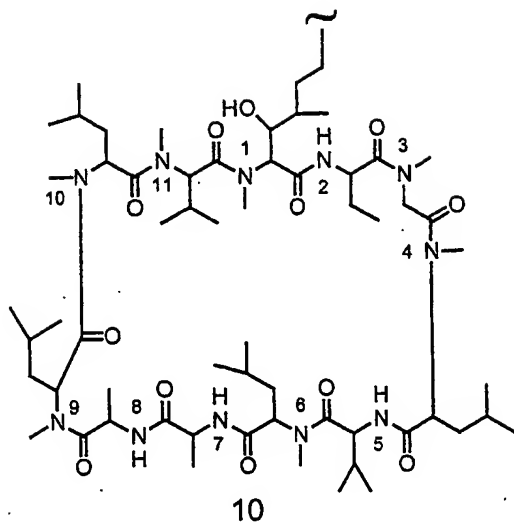
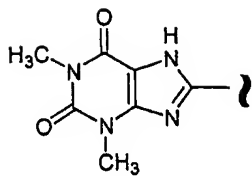
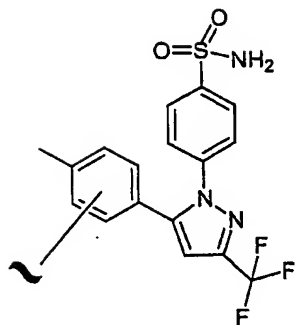


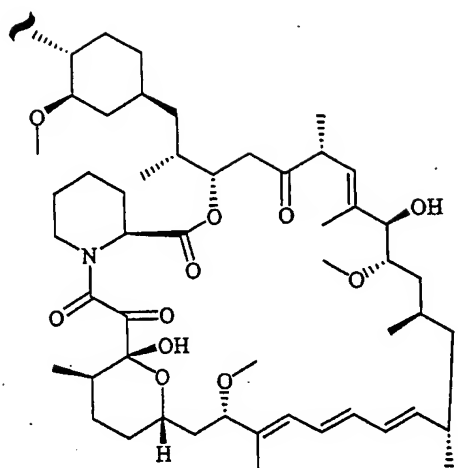
Table 1.4

11

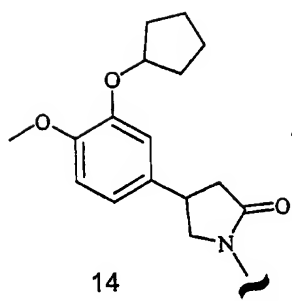


12

Table 1.5

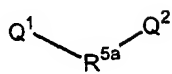


13

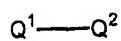


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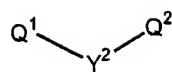
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Table 10.I

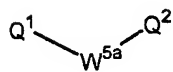
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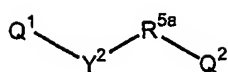
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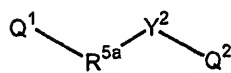
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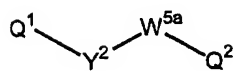
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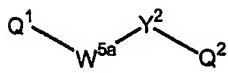
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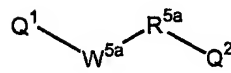
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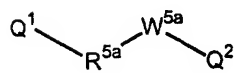
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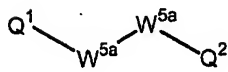
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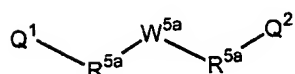
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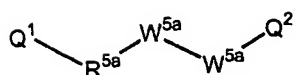
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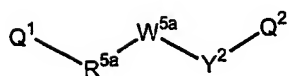
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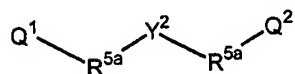
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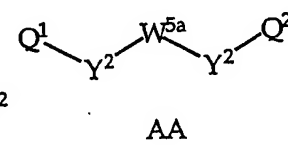
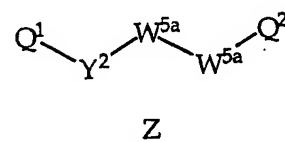
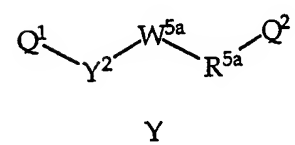
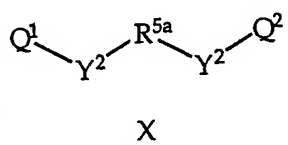
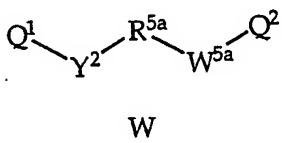
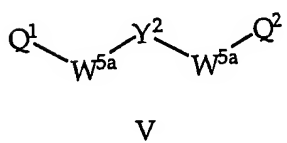
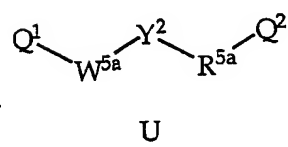
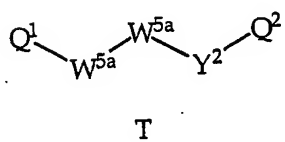
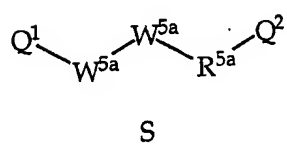
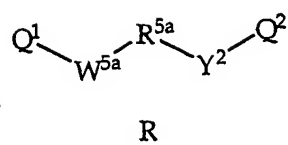
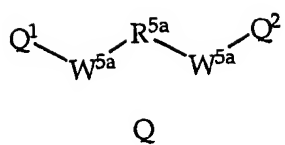
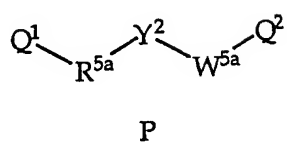
Table 10.2

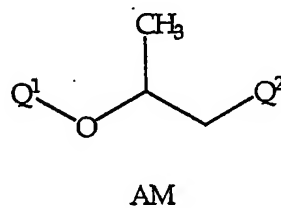
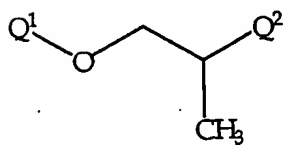
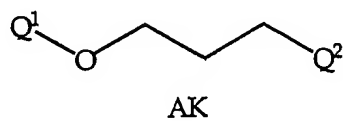
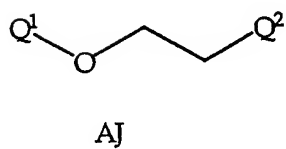
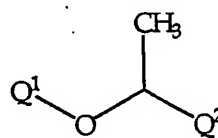
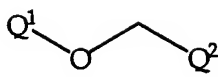
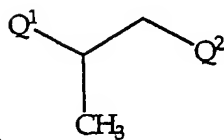
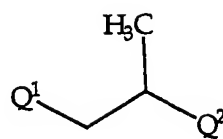
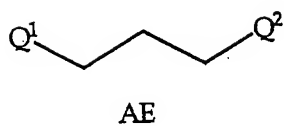
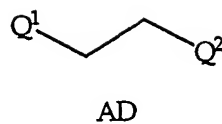
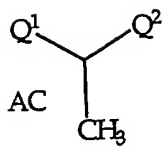
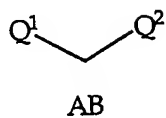
Table 10.3

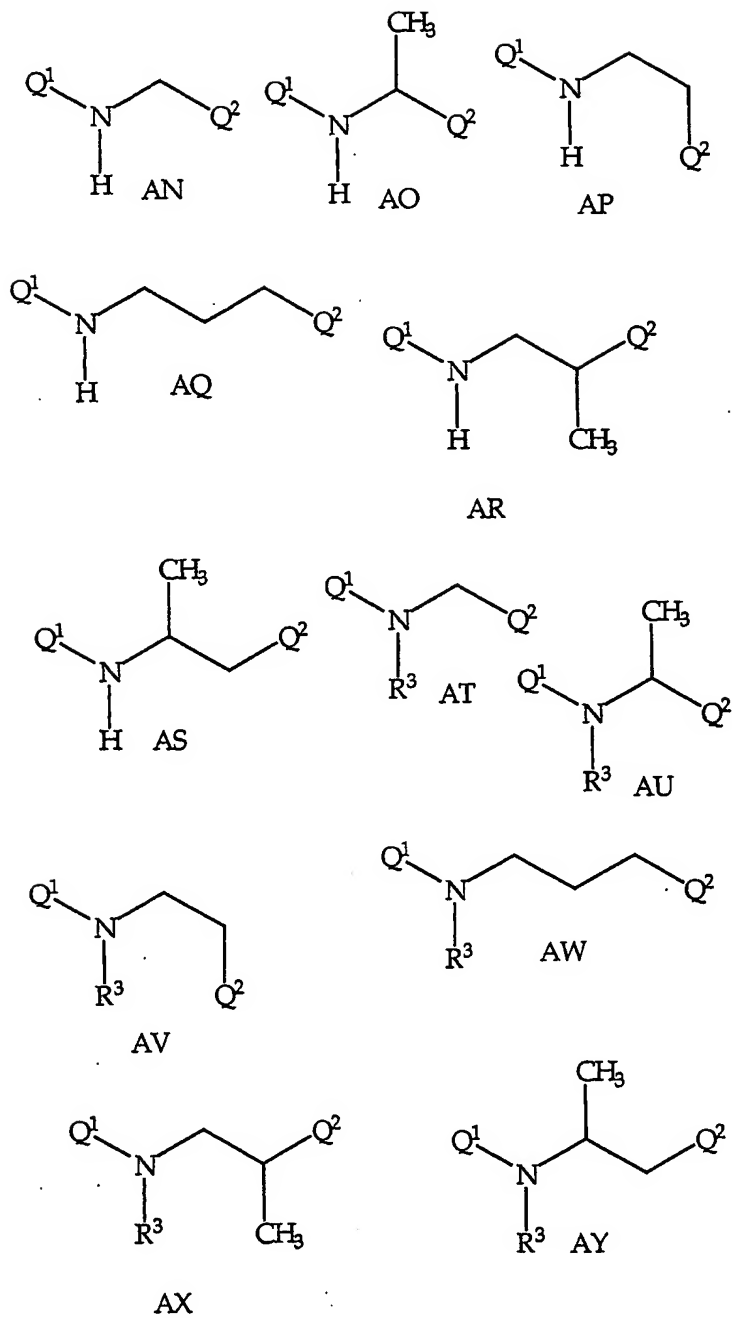
Table 10.4

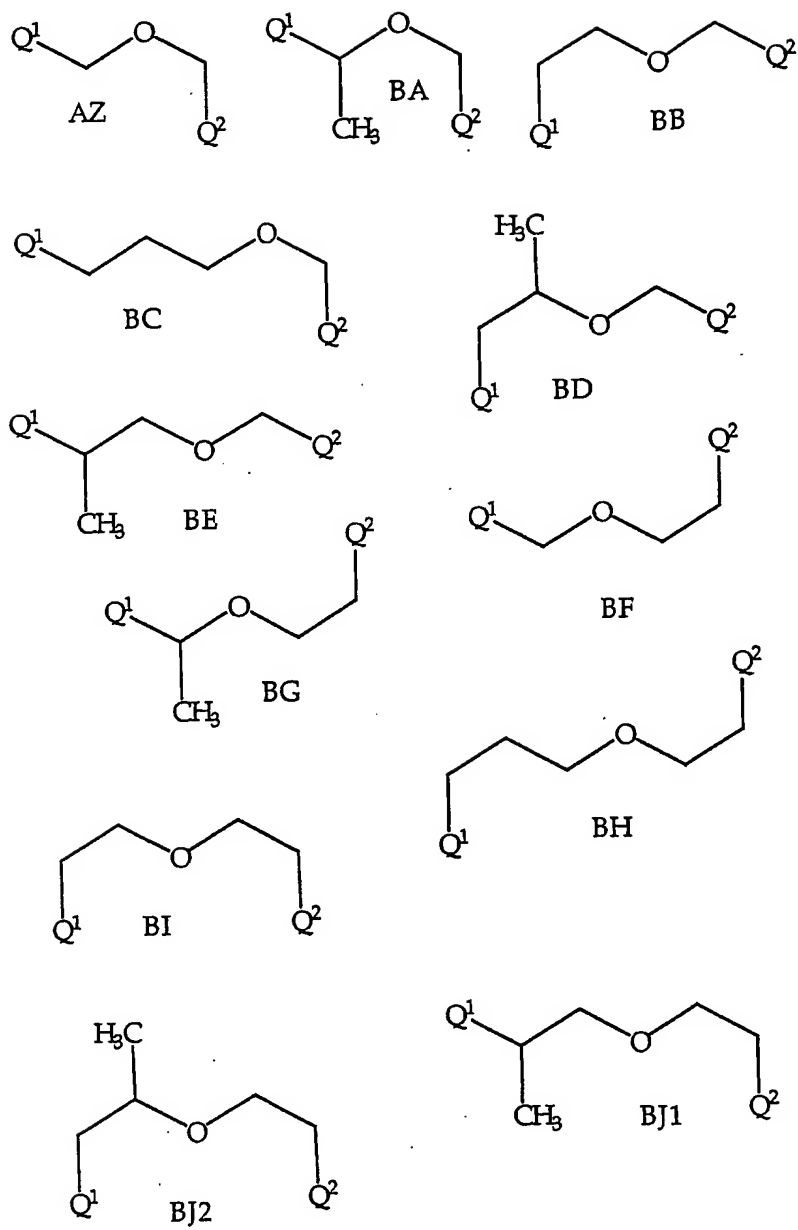
Table 10.5

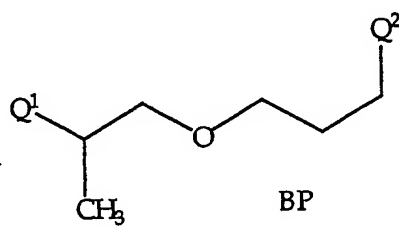
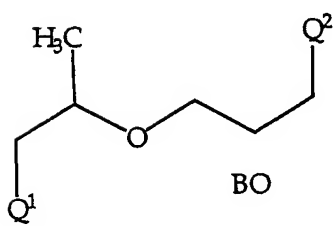
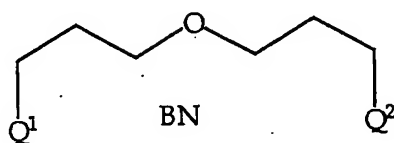
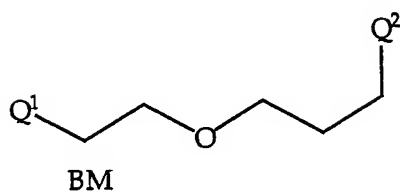
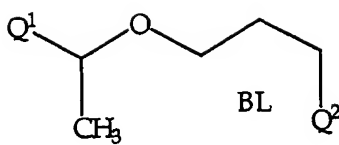
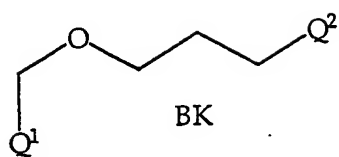
Table 10.6

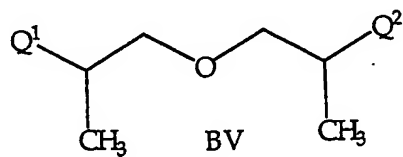
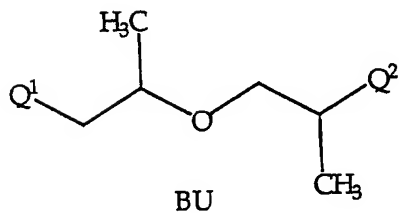
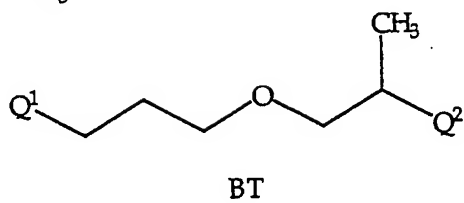
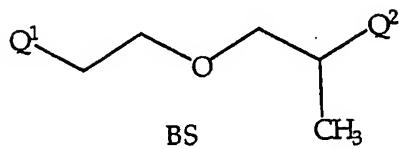
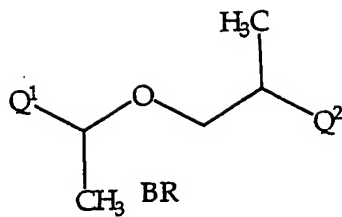
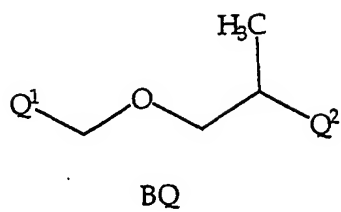
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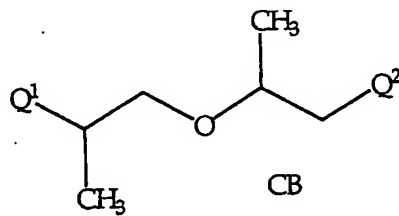
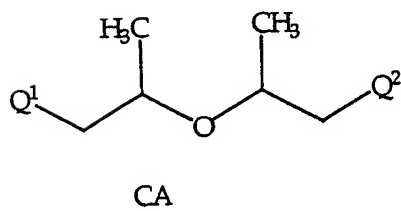
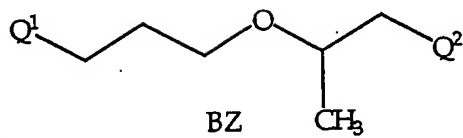
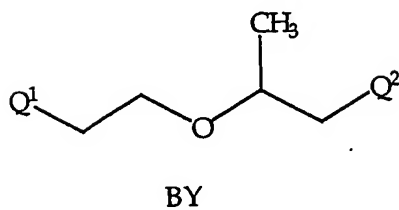
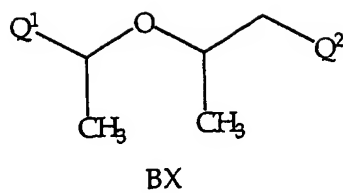
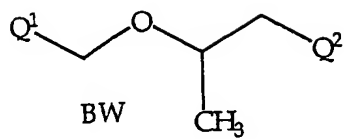
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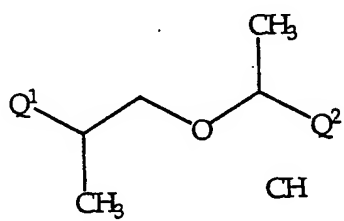
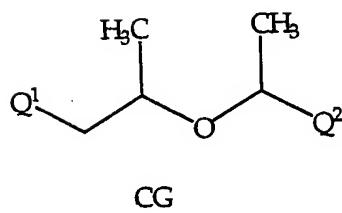
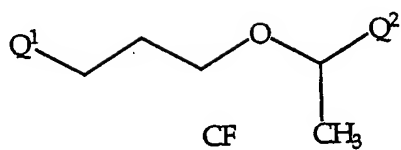
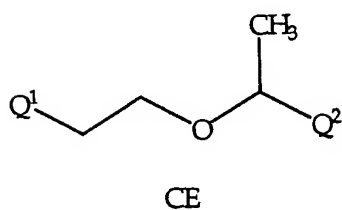
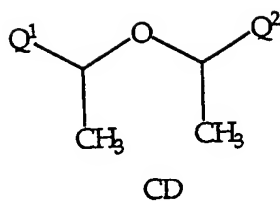
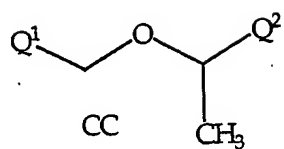
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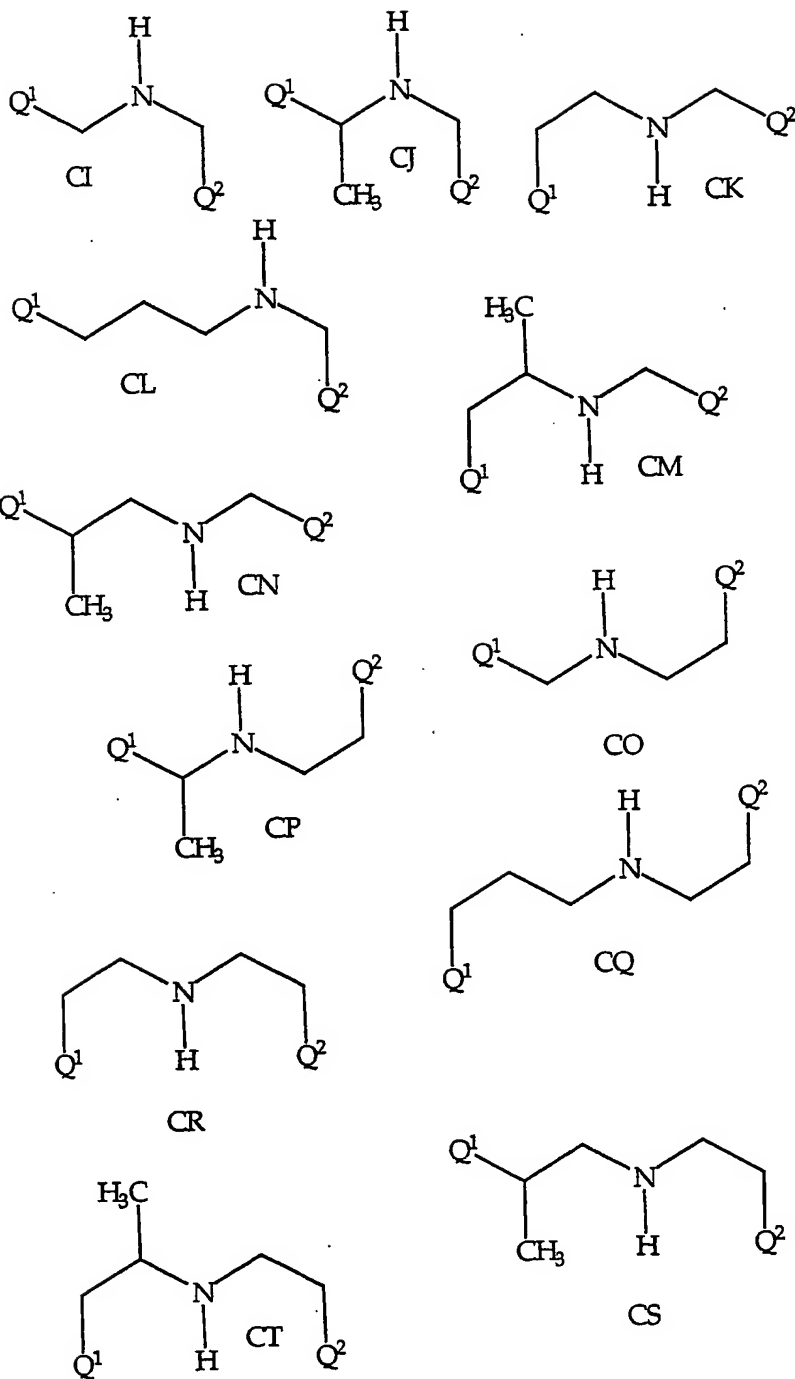
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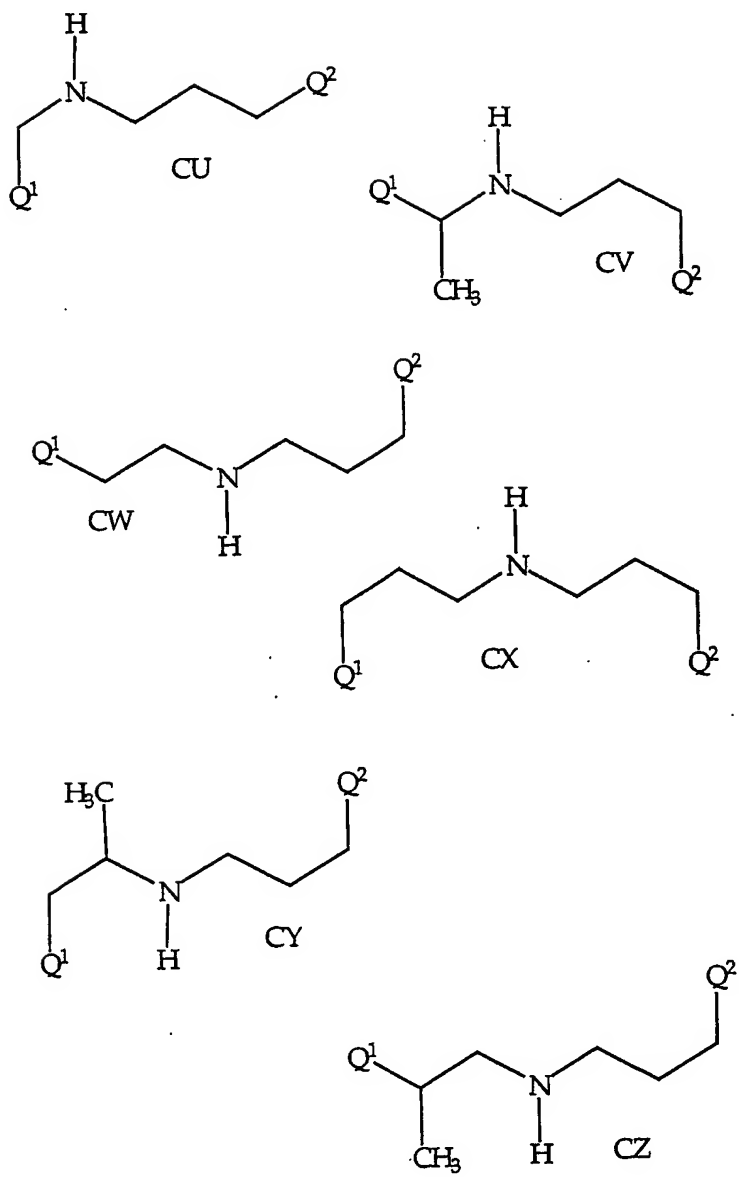
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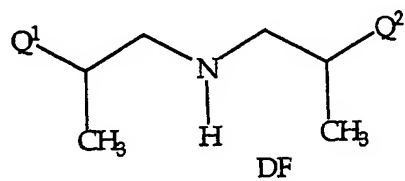
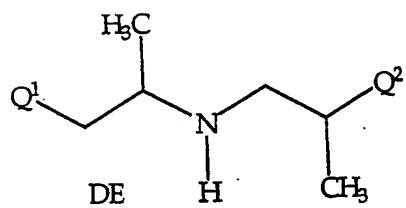
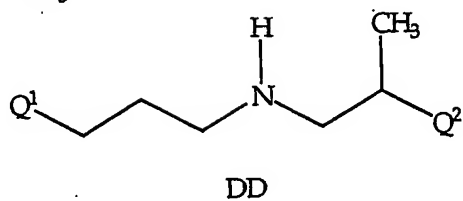
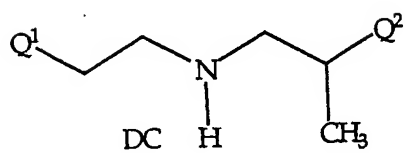
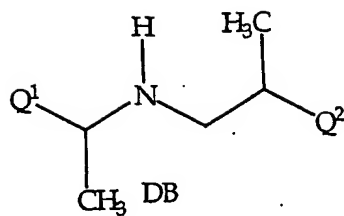
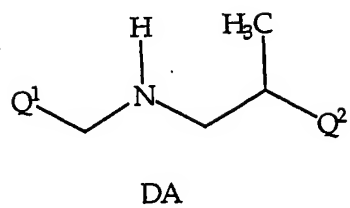
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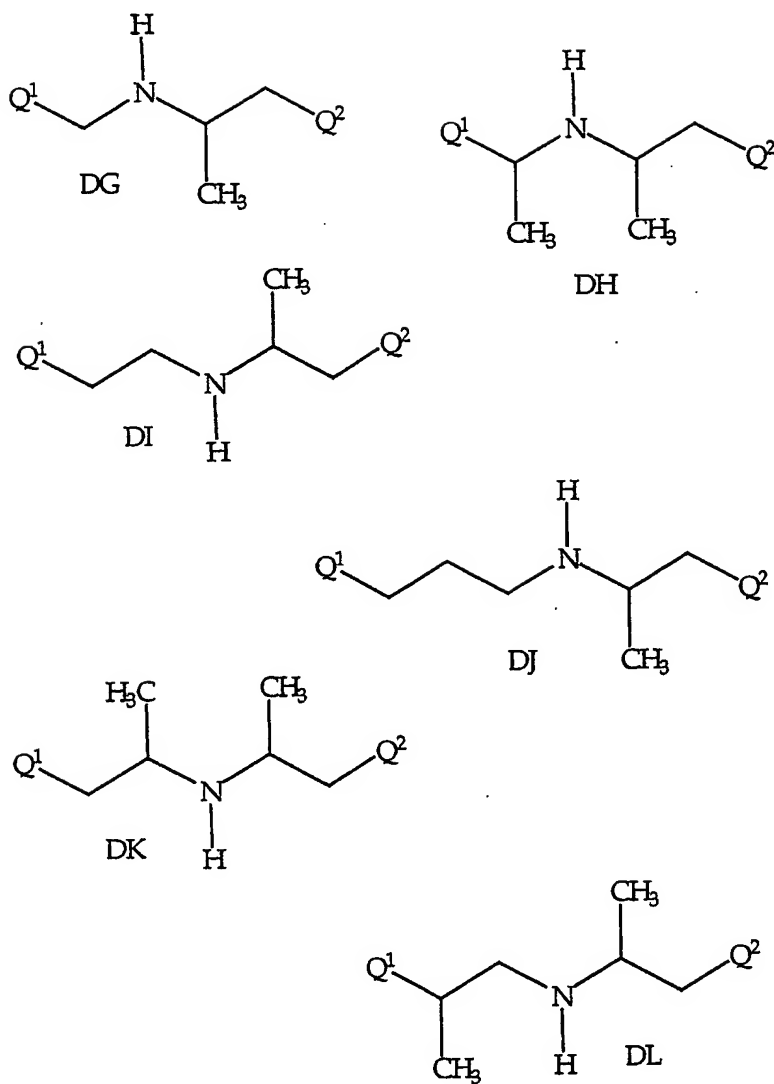
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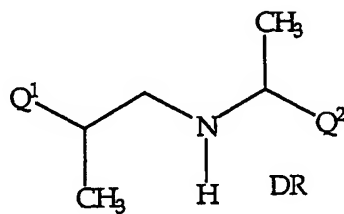
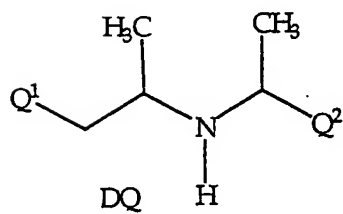
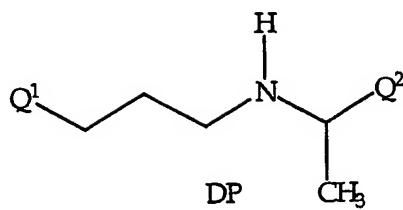
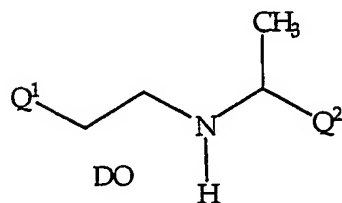
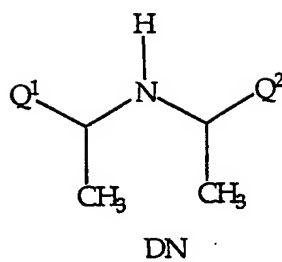
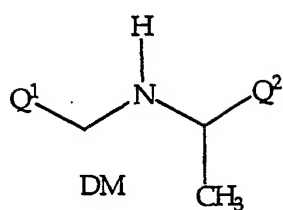
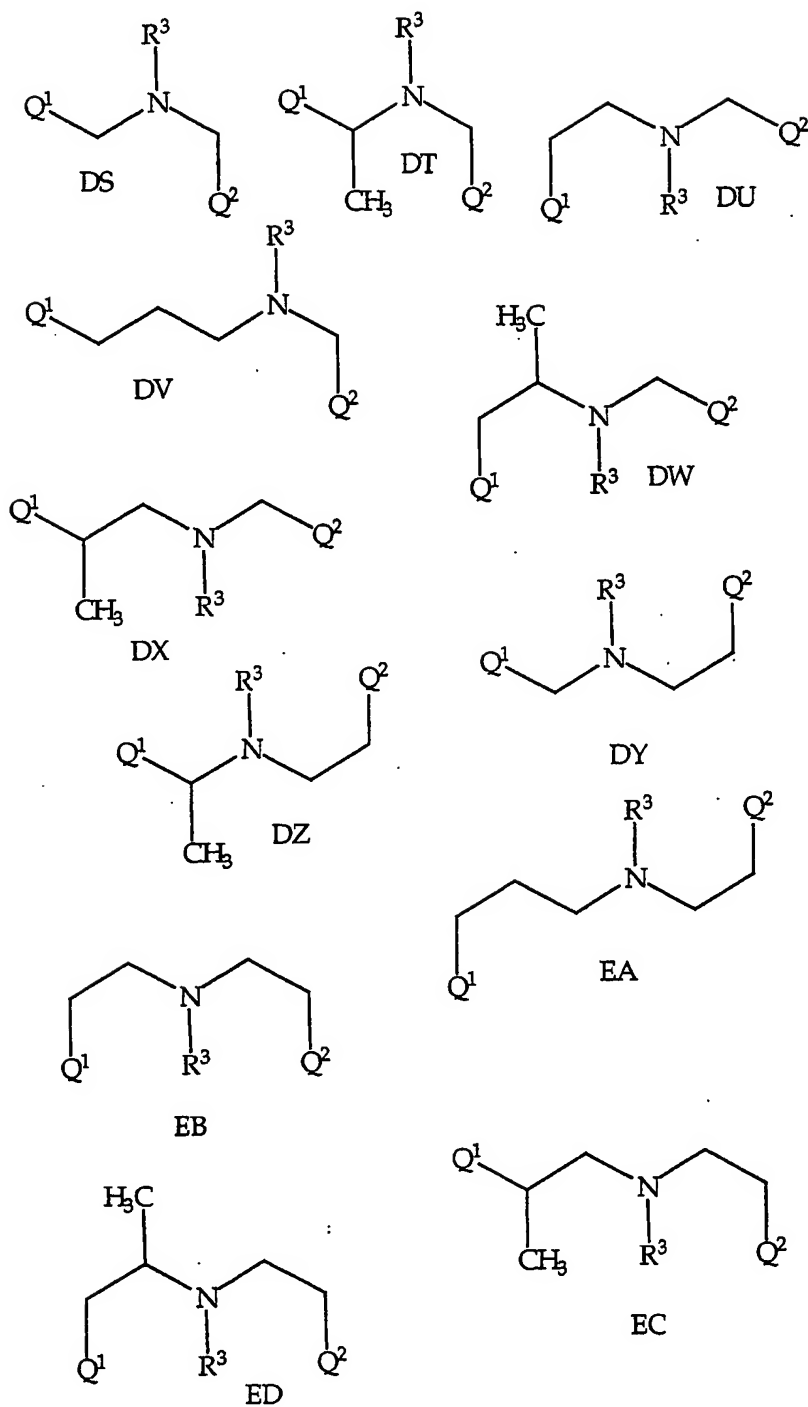
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Table 10.15



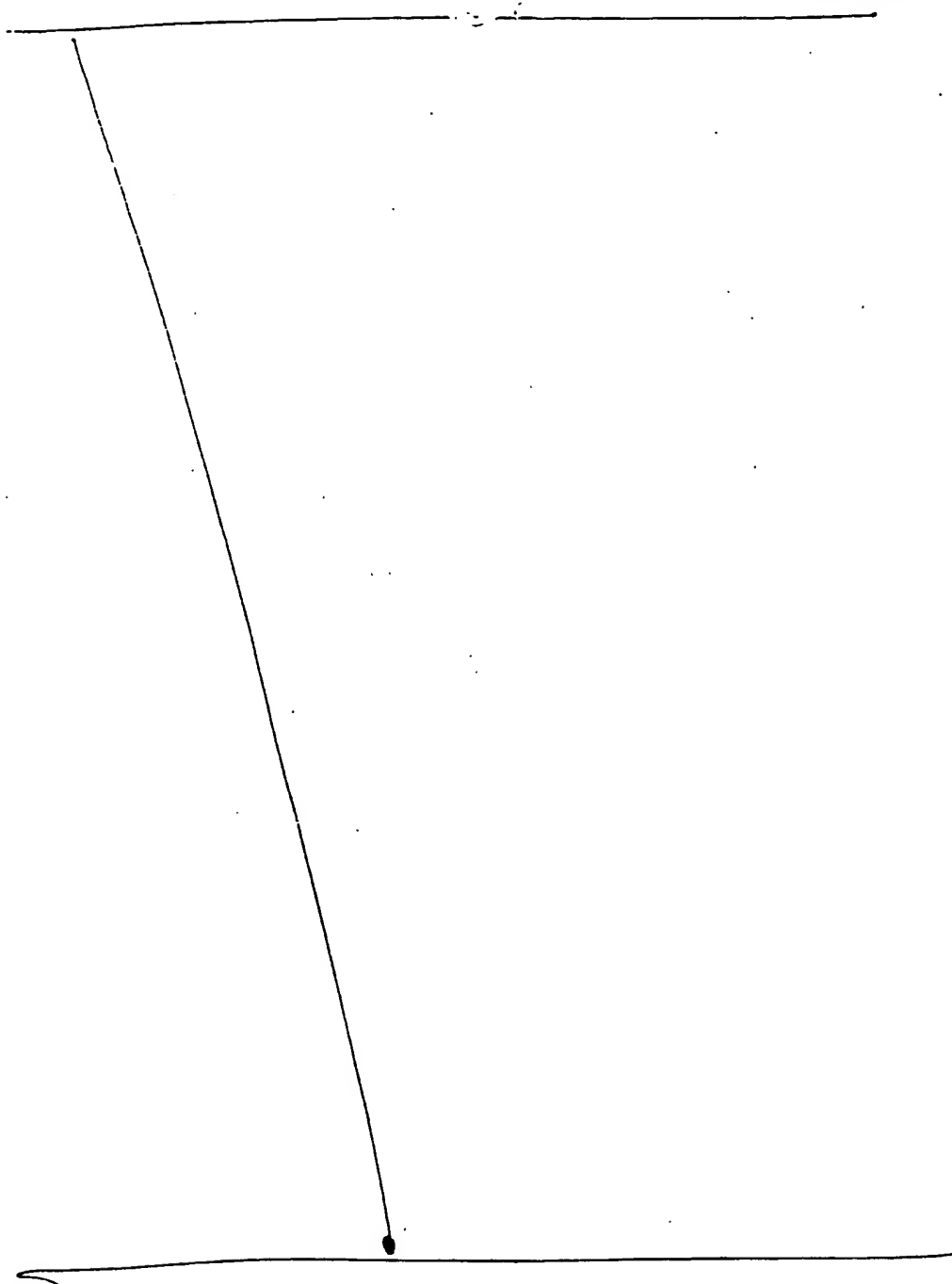


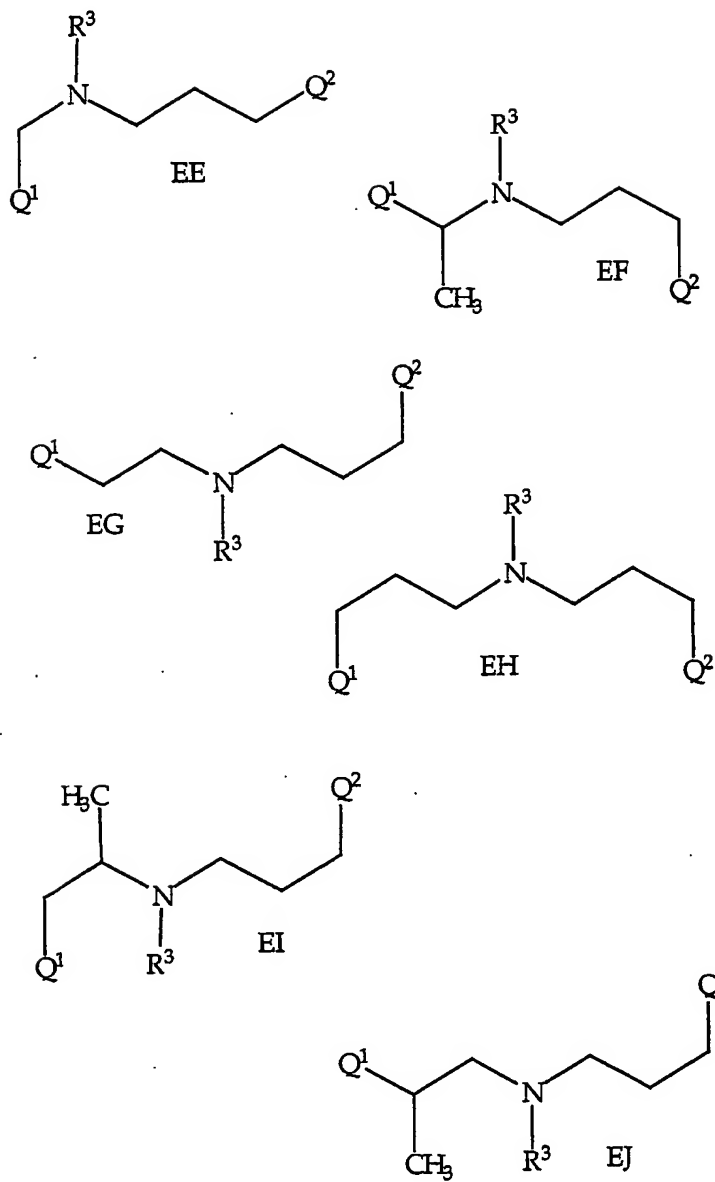
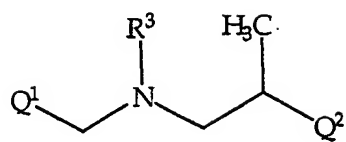
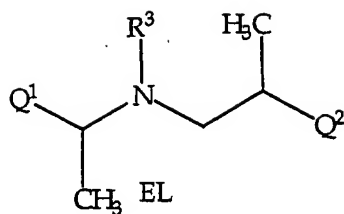
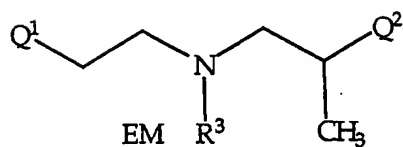
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Table 10.17

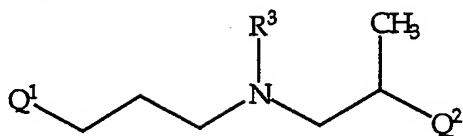
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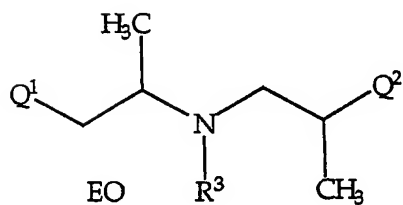
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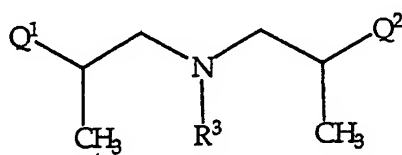
EM



EN



EO



EP

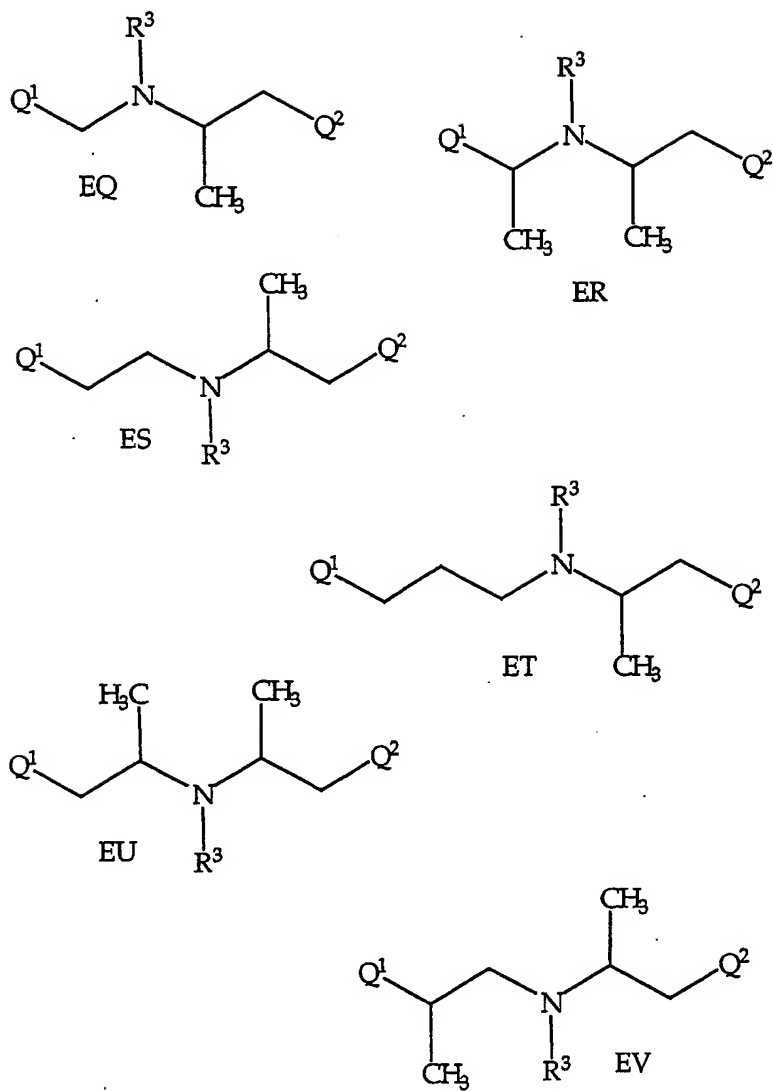
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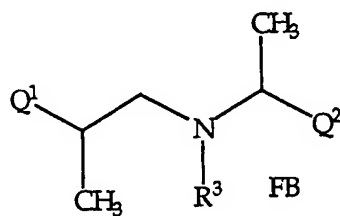
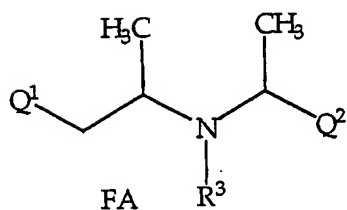
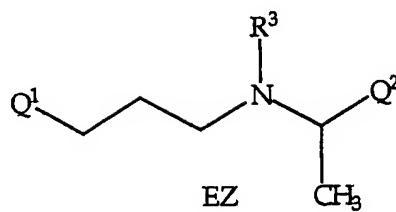
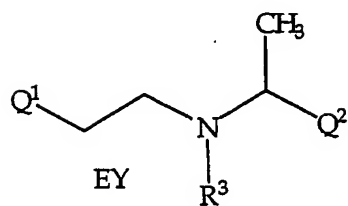
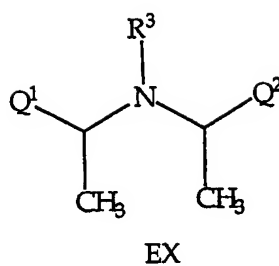
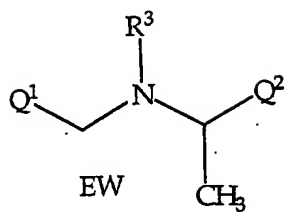
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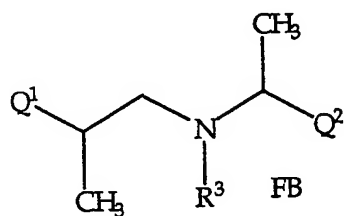
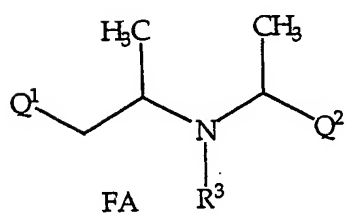
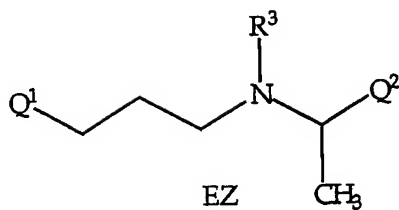
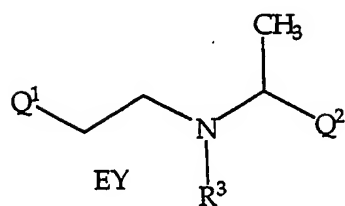
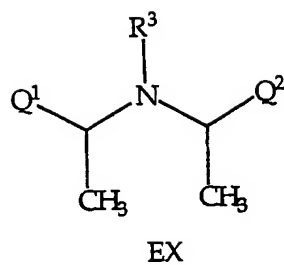
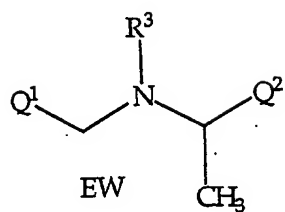
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Table 20.1

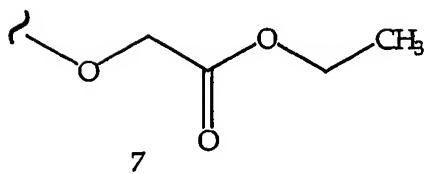
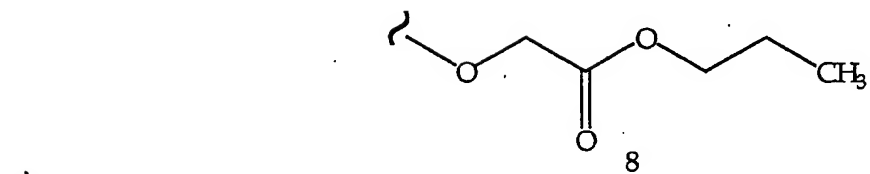
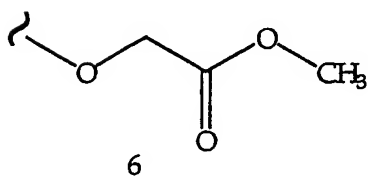
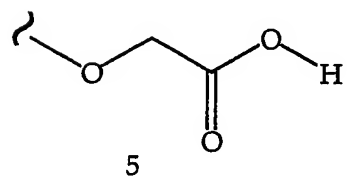
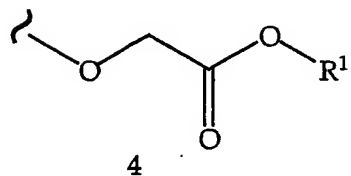
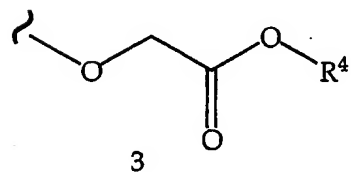
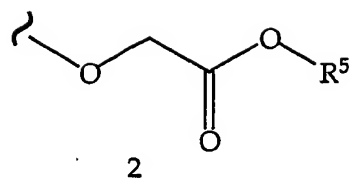
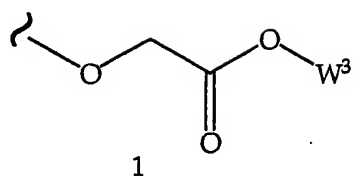
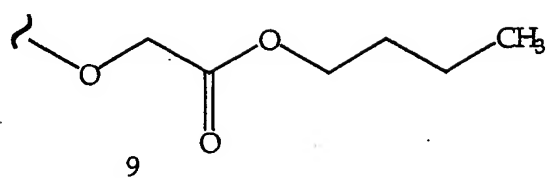
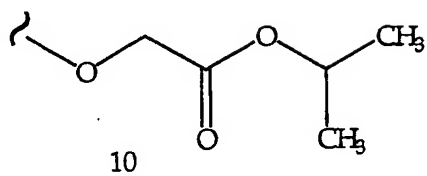
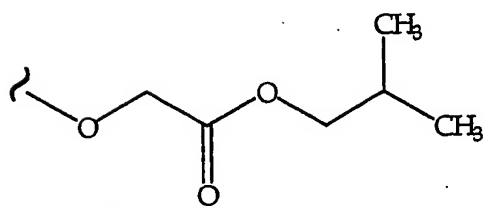


Table 20.2

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11

Table 20.3

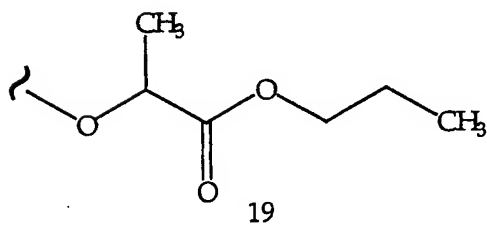
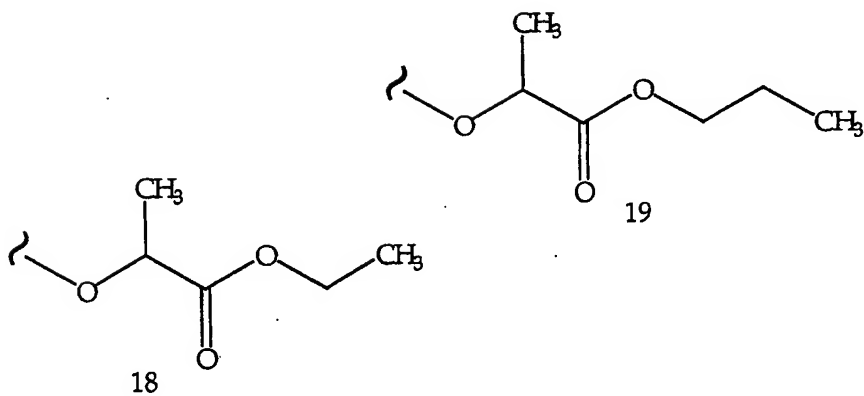
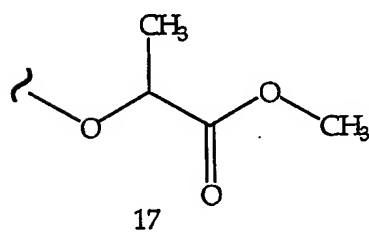
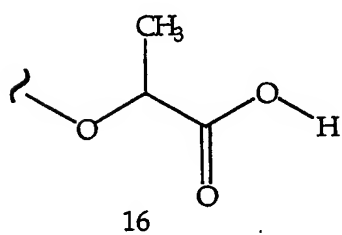
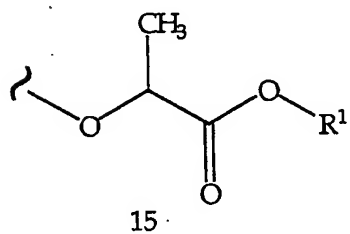
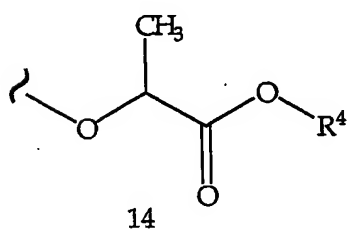
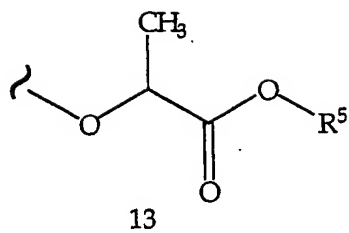
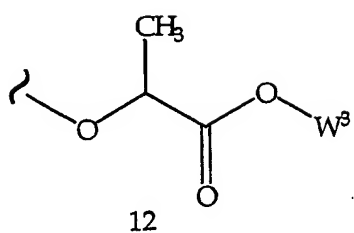


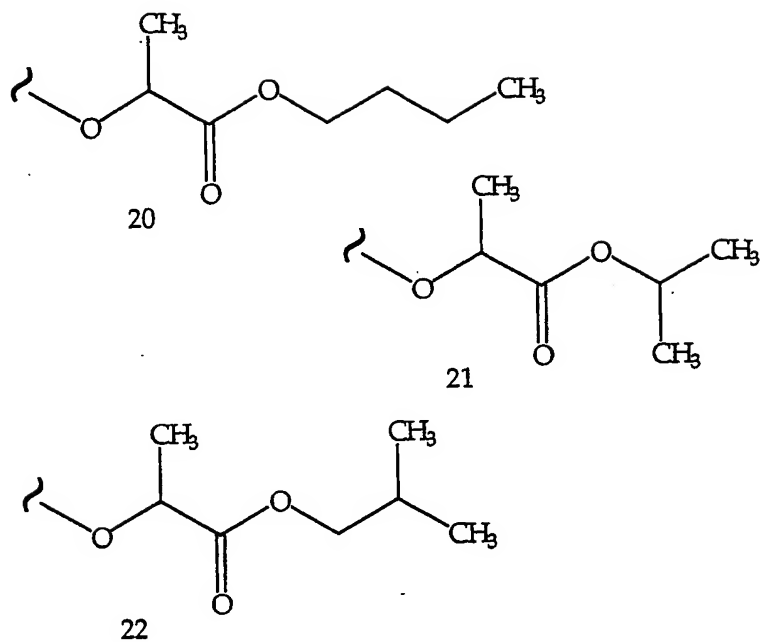
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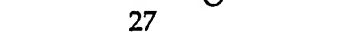
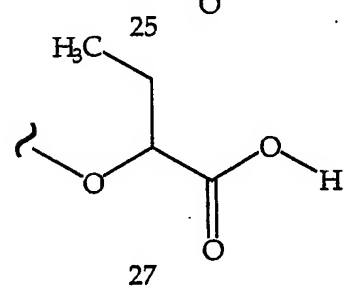
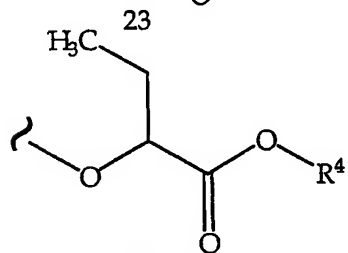
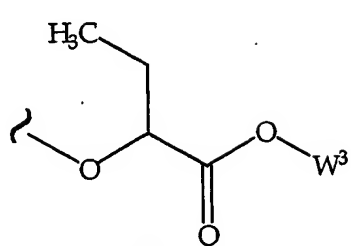
Table 20.5

Table 20.6

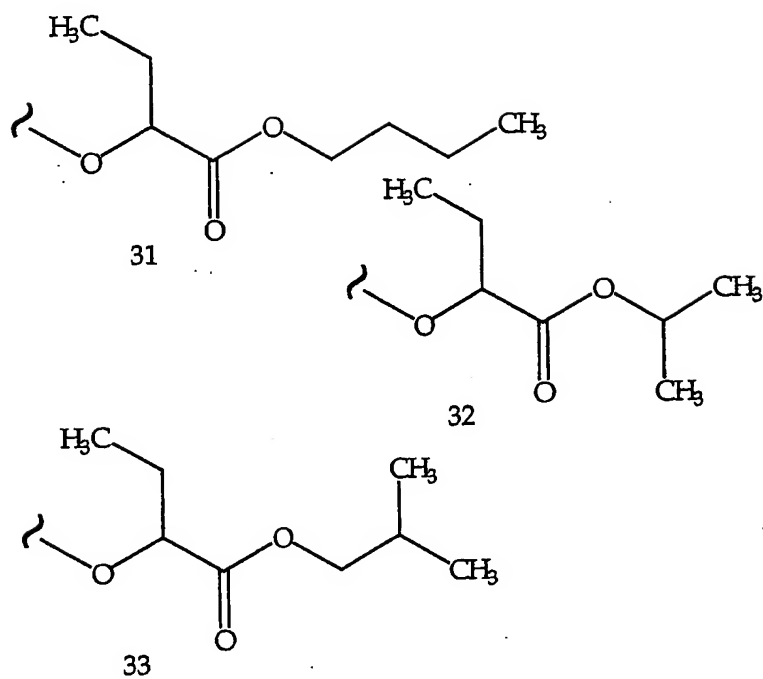


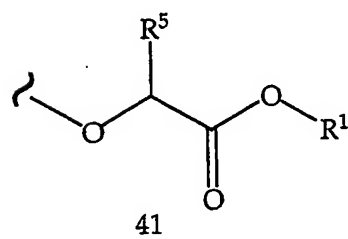
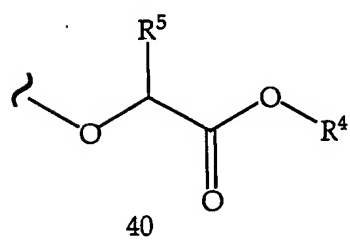
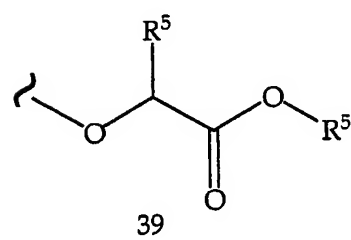
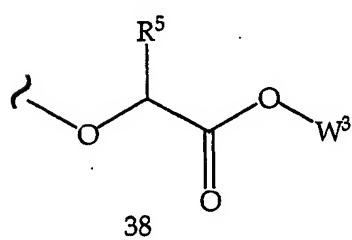
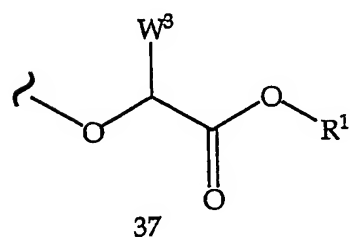
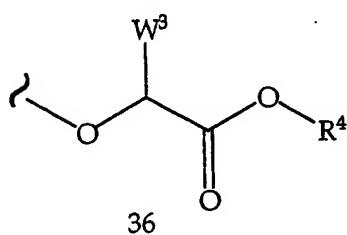
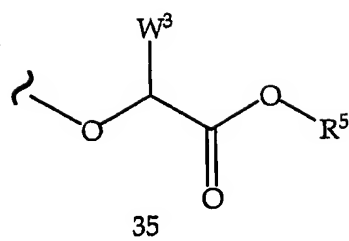
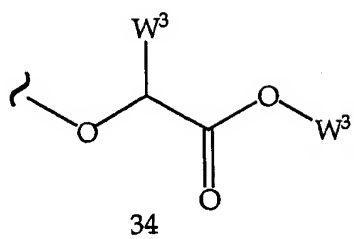
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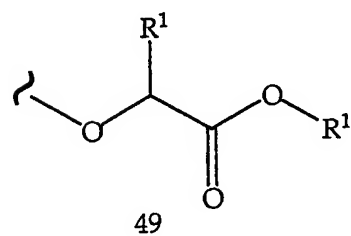
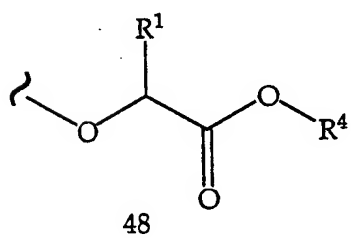
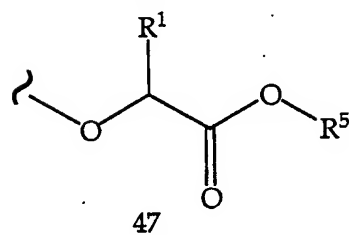
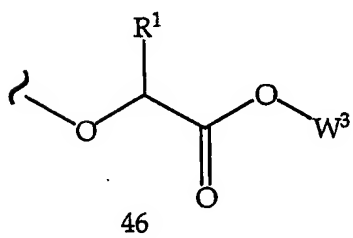
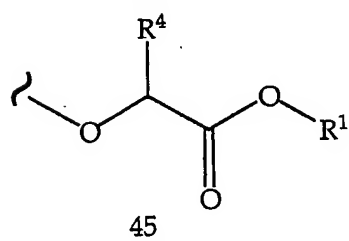
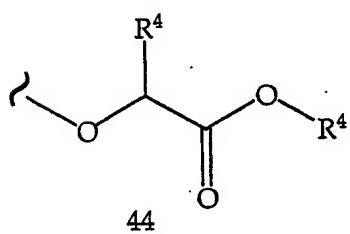
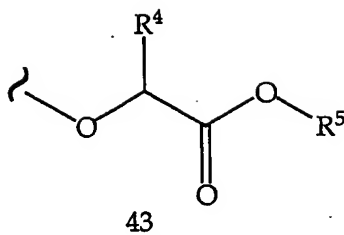
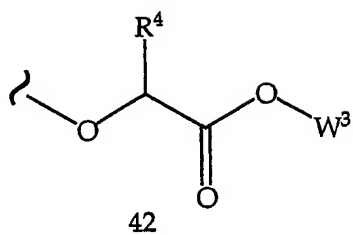
Table 20.8

Table 20.9

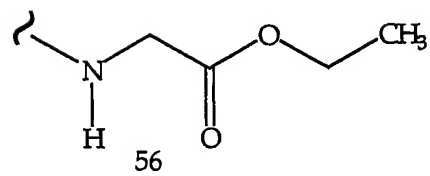
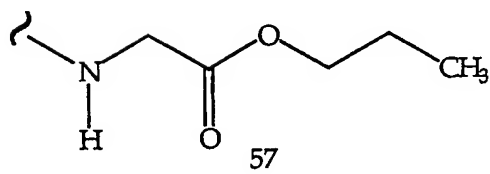
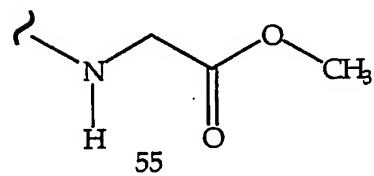
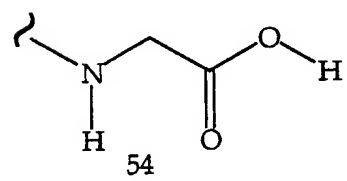
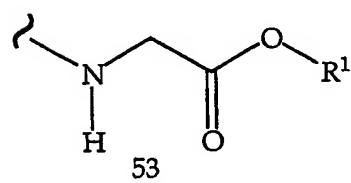
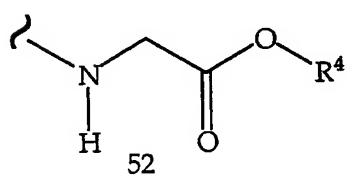
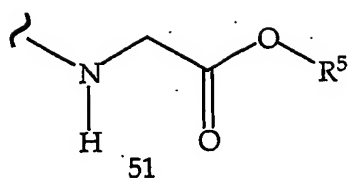
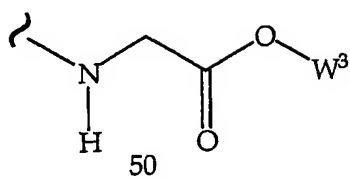


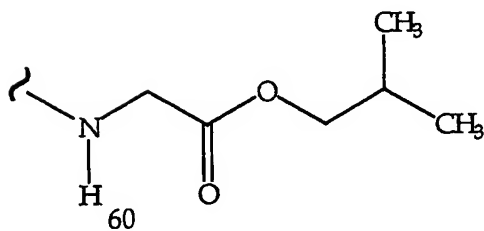
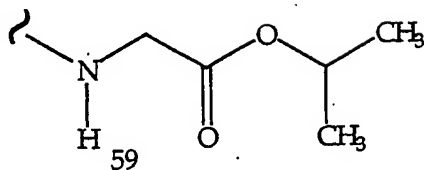
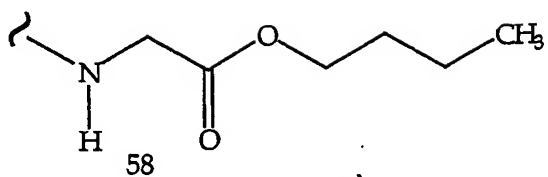
Table 20.10

Table 20.11

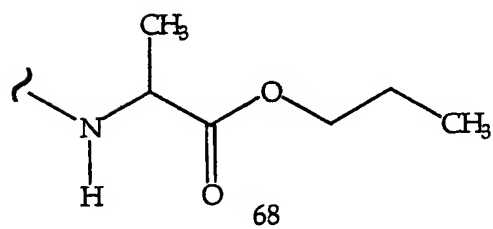
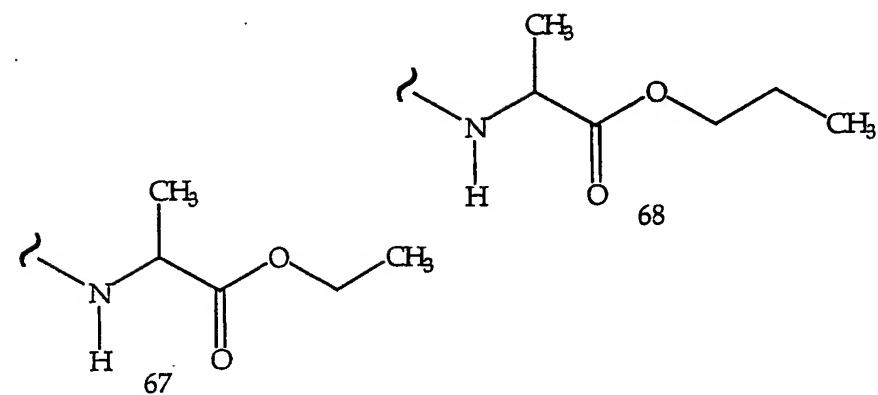
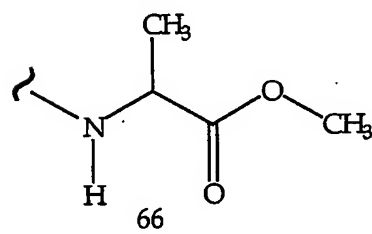
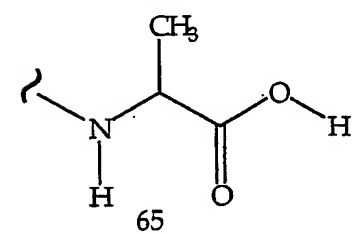
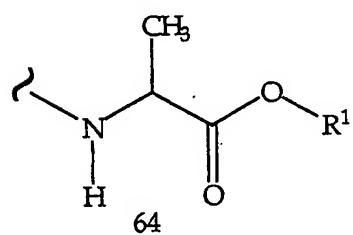
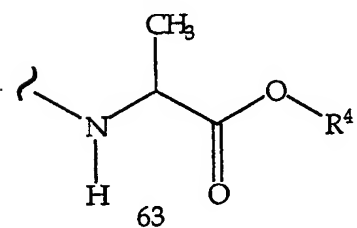
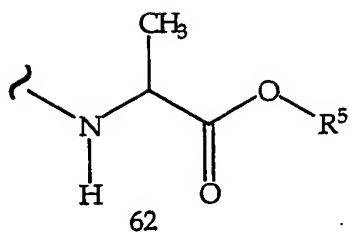
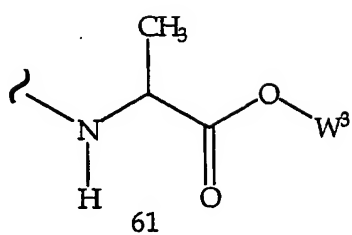


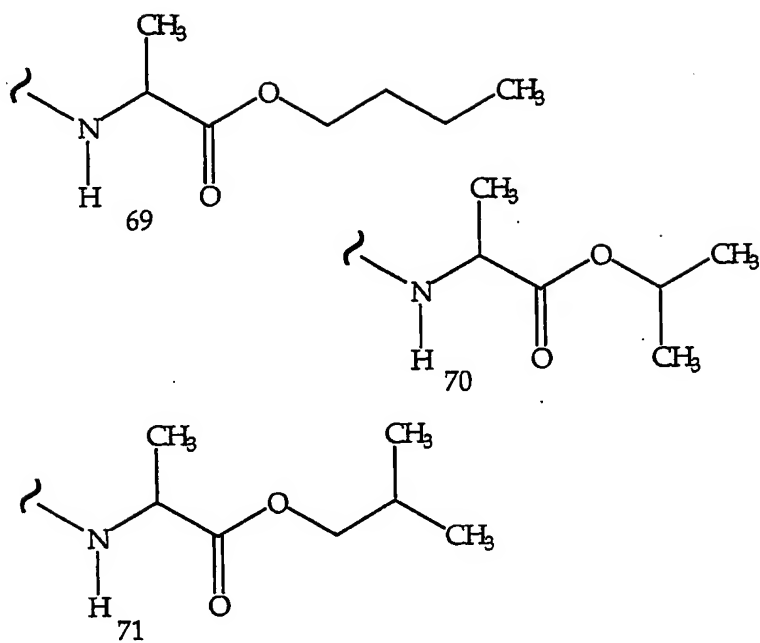
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Table 20.13

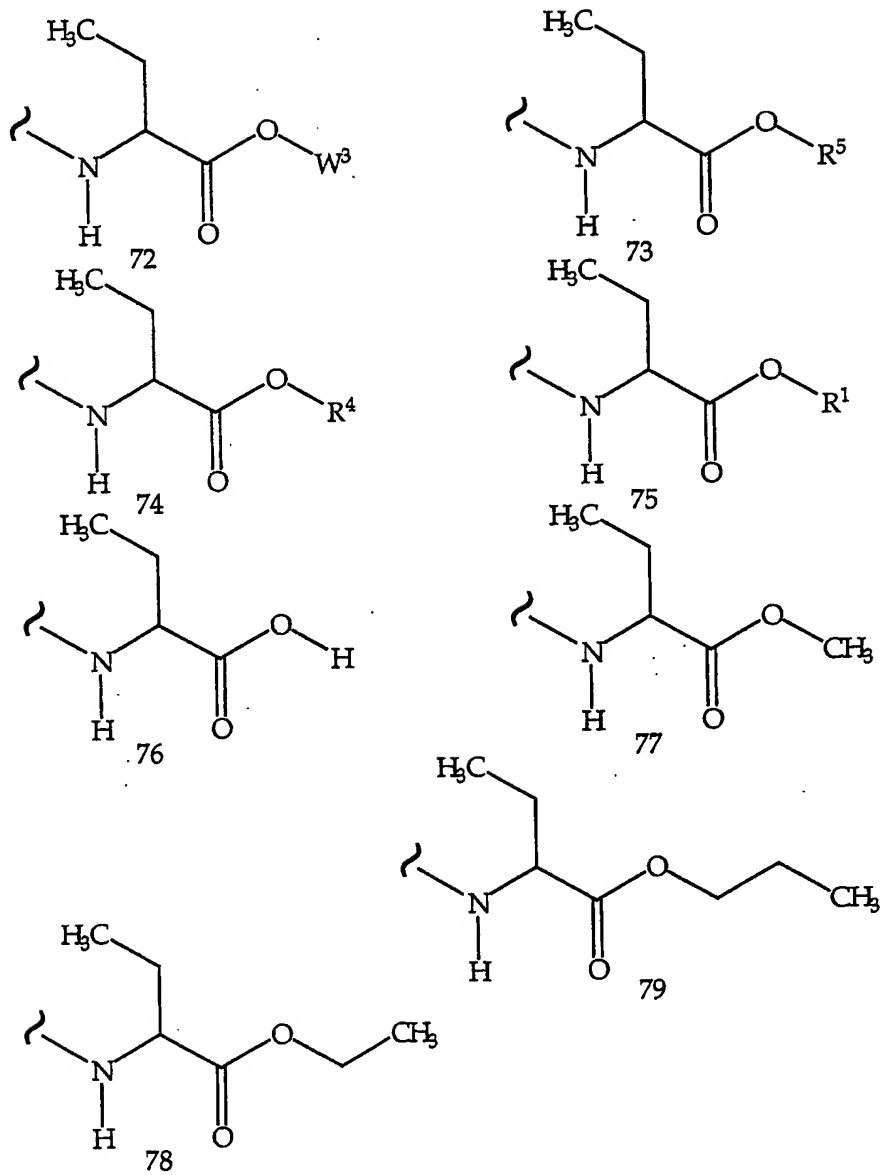


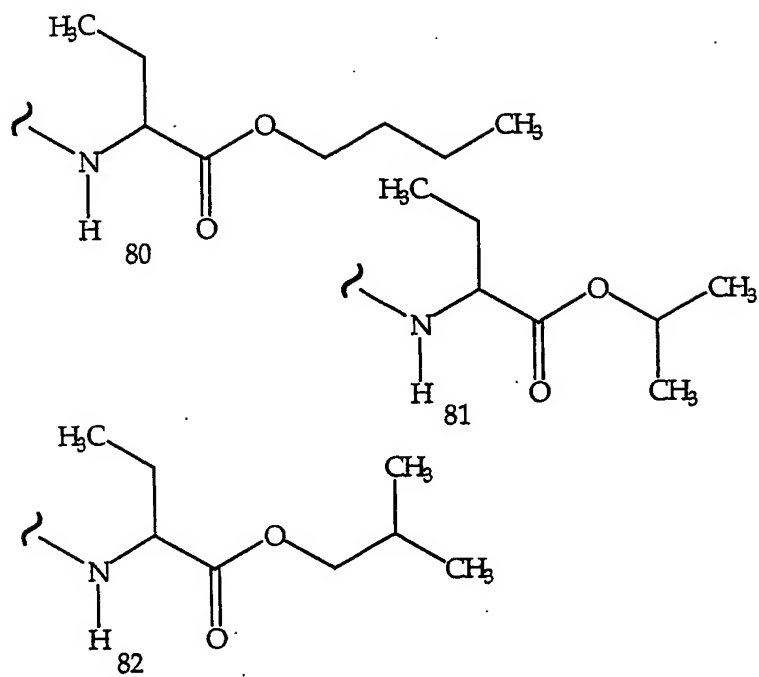
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Table 20.15

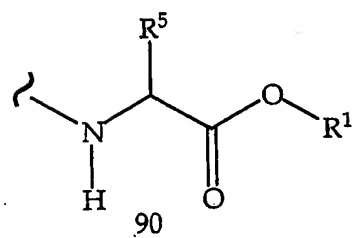
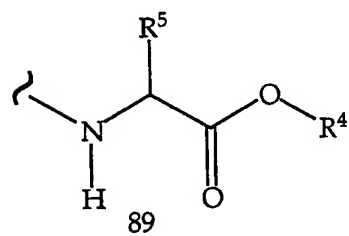
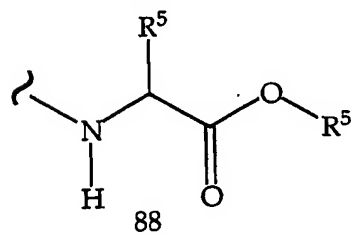
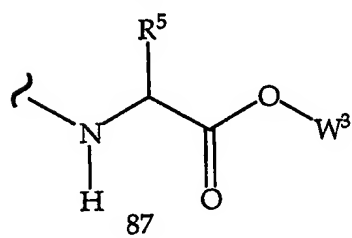
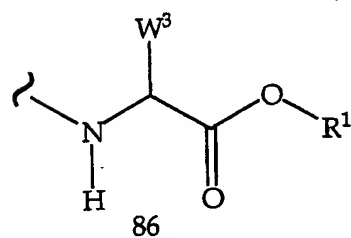
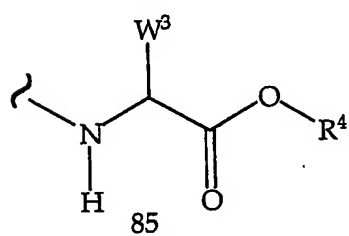
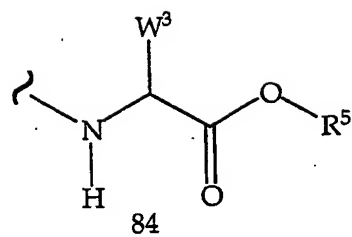
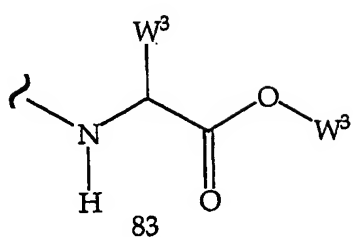


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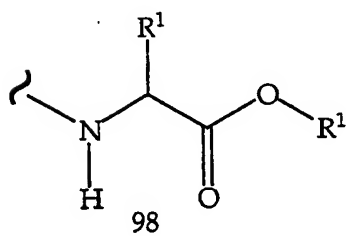
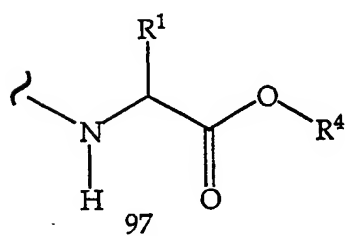
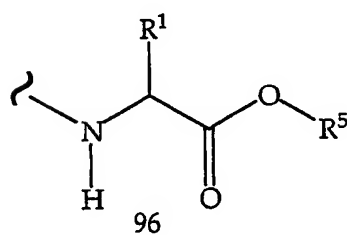
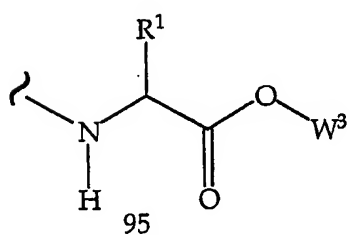
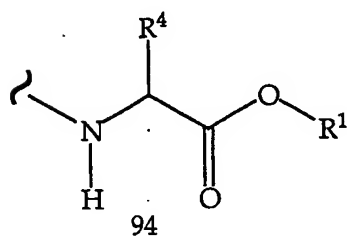
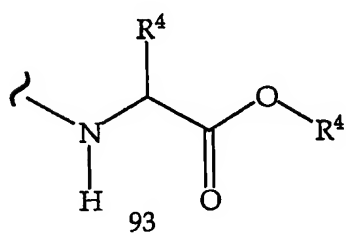
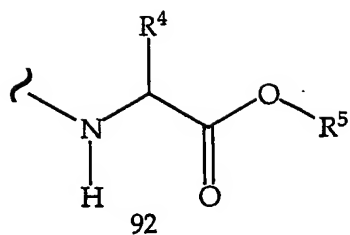
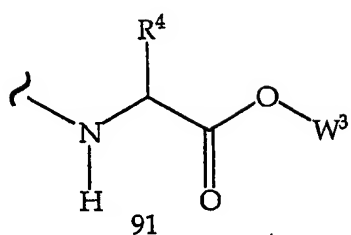


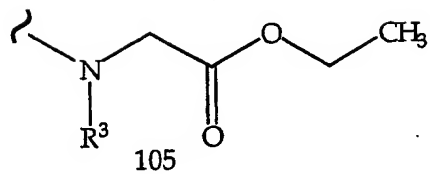
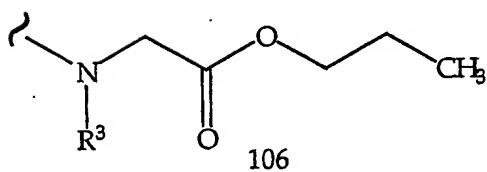
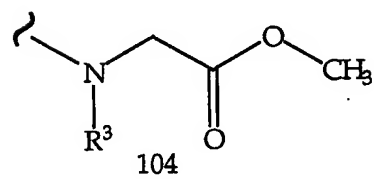
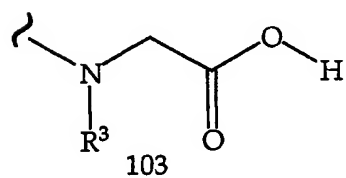
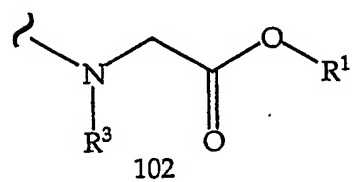
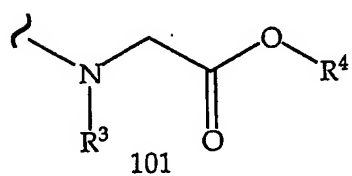
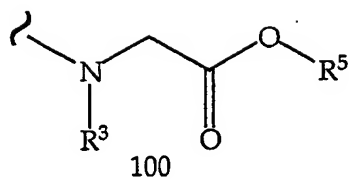
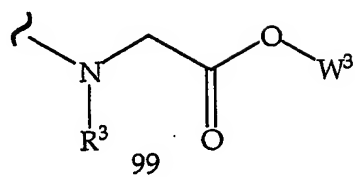
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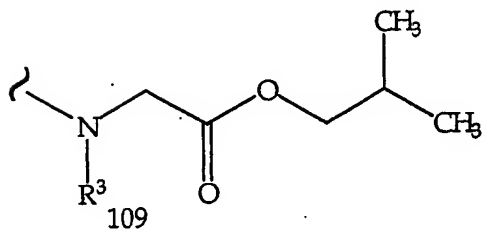
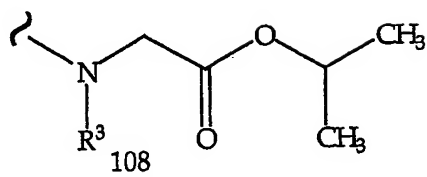
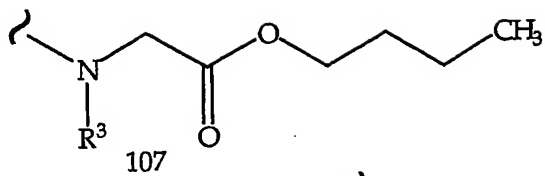
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Table 20.19

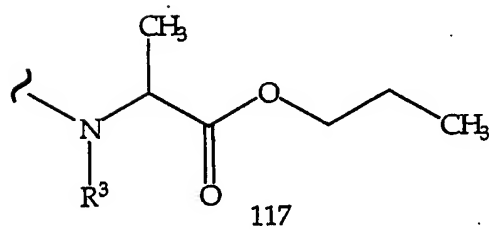
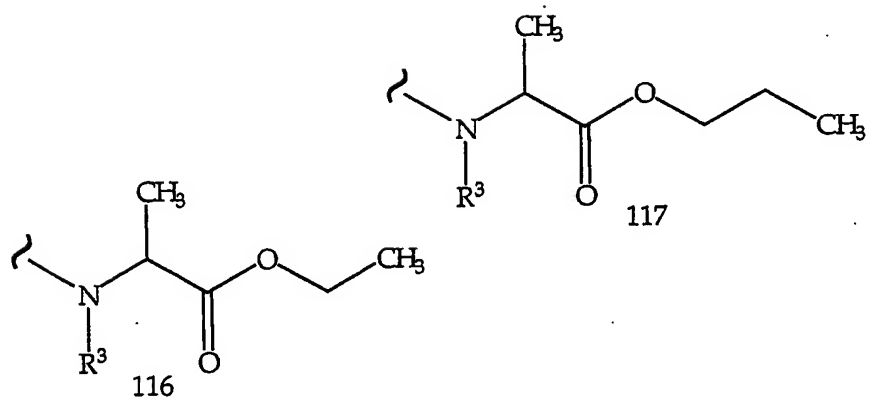
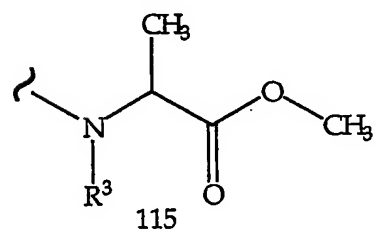
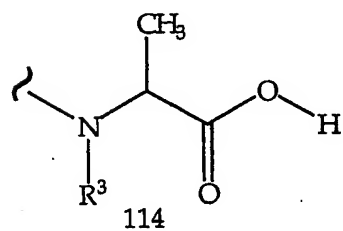
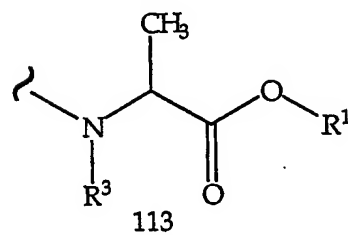
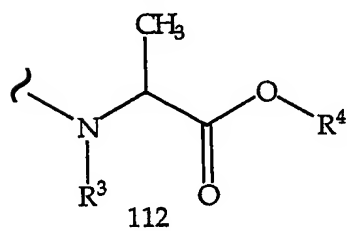
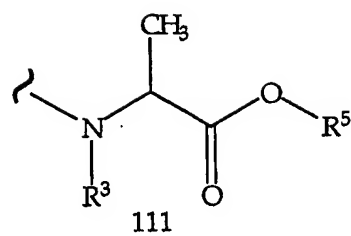
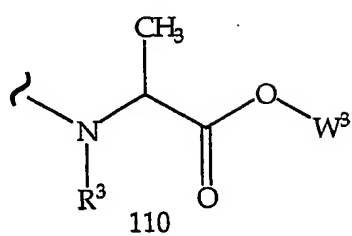


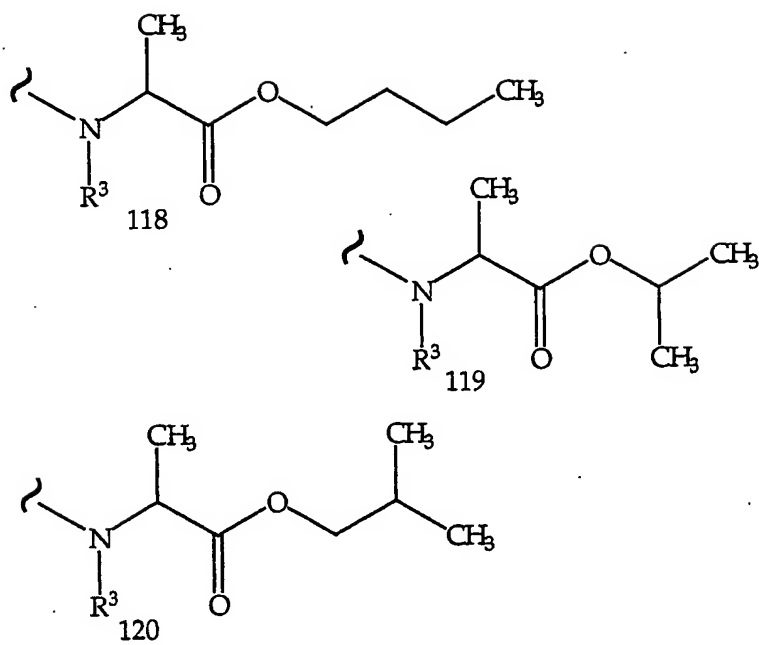
Table 20.20

Table 20.21

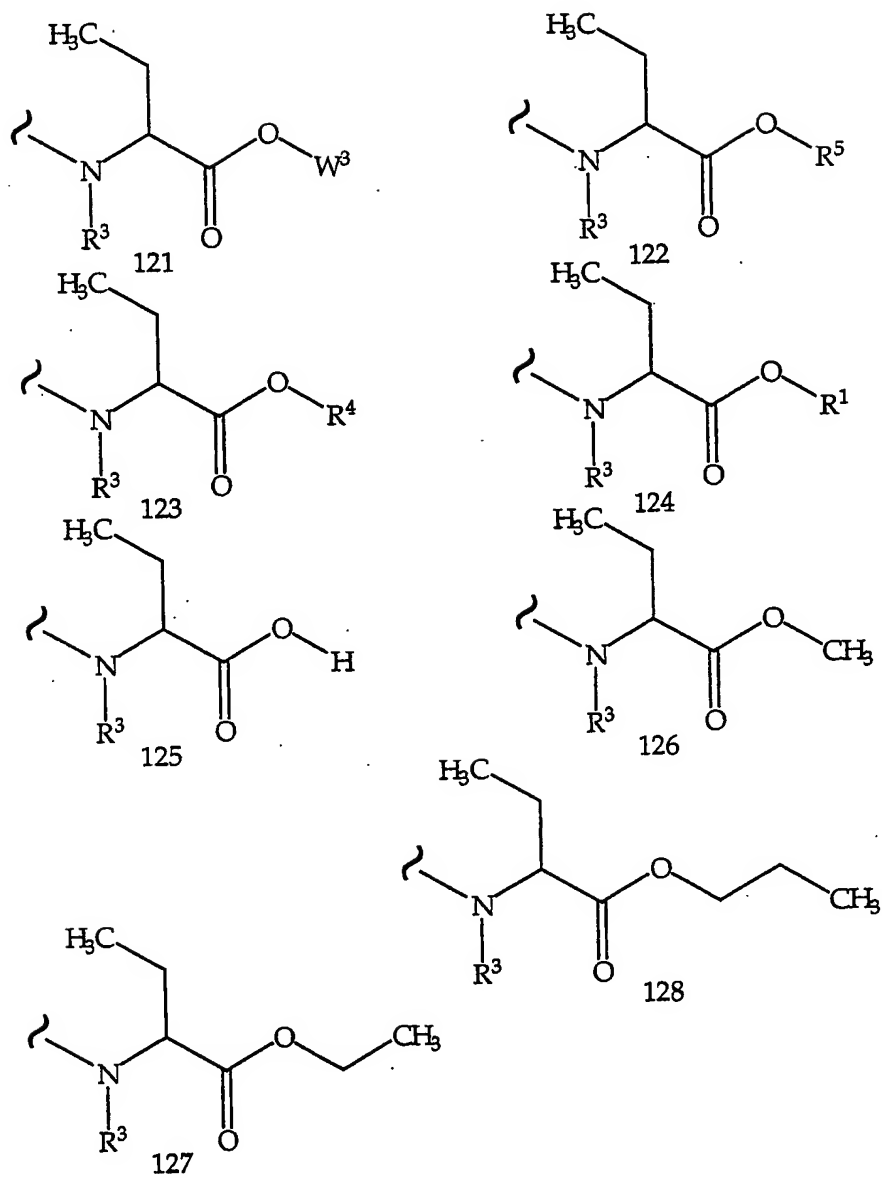


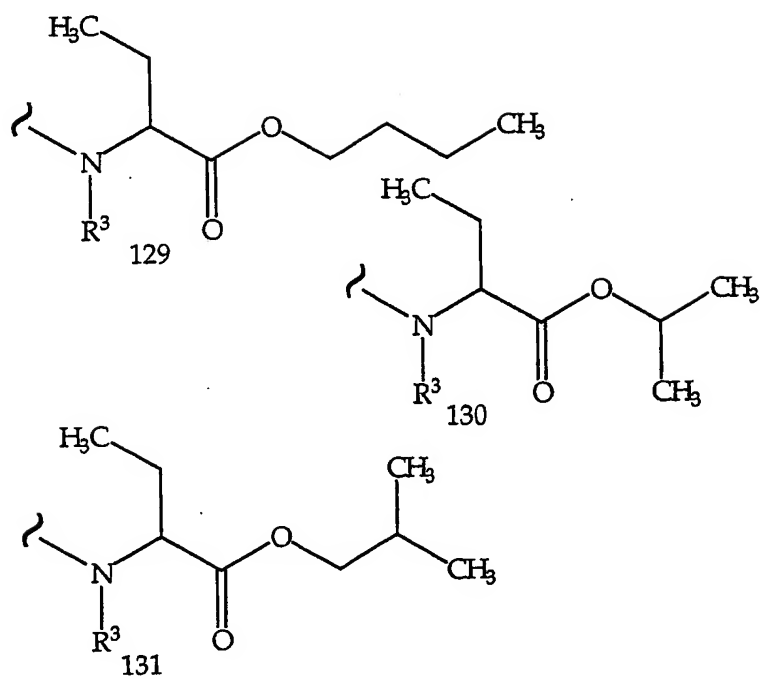
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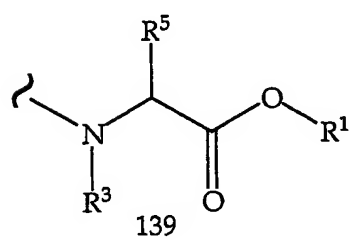
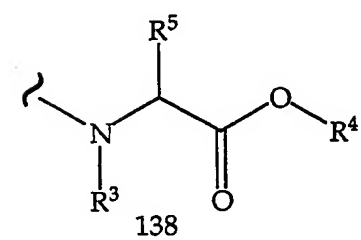
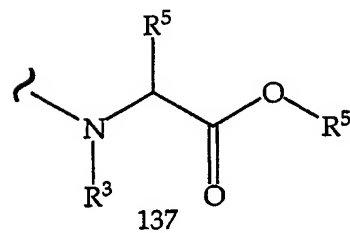
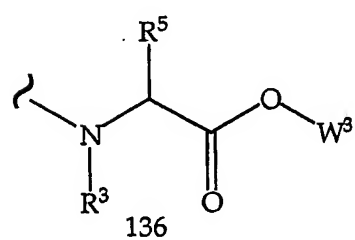
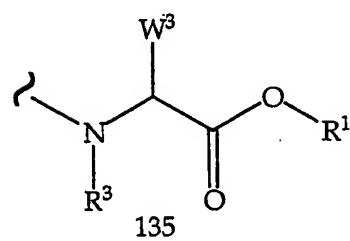
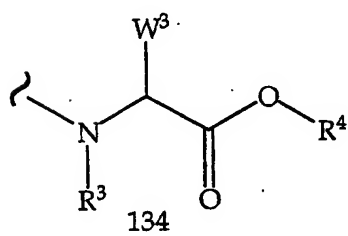
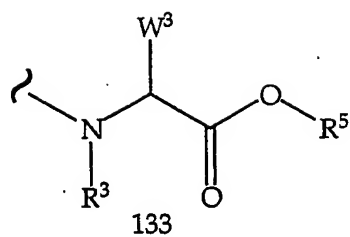
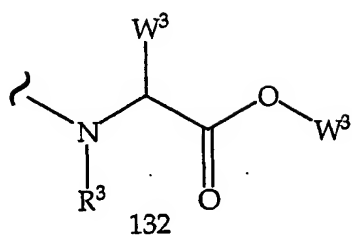
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Table 20.24

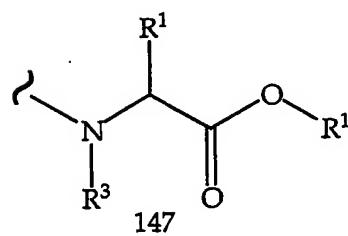
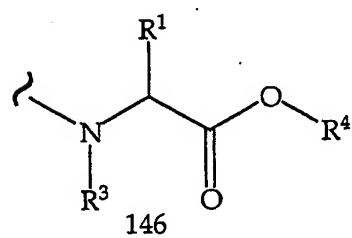
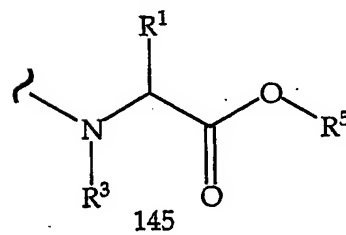
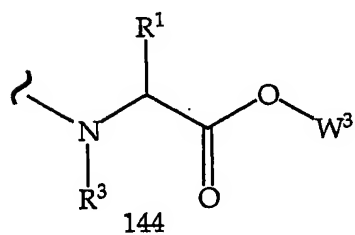
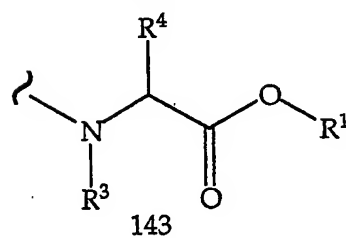
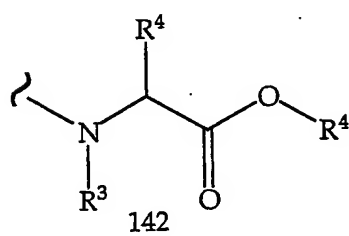
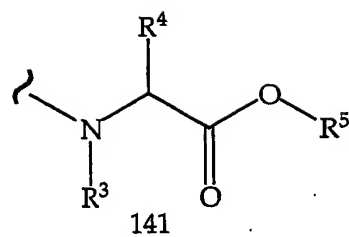
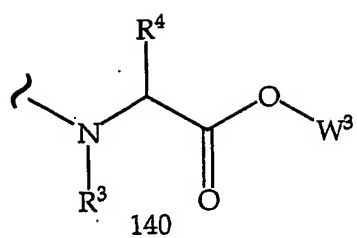
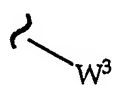
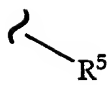
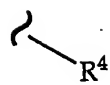


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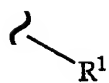
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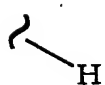
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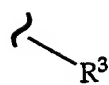
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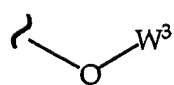
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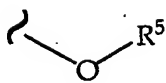
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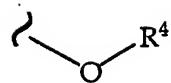
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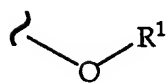
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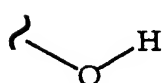
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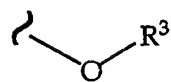
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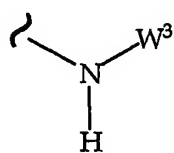
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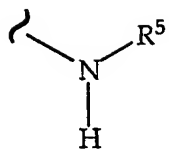
158



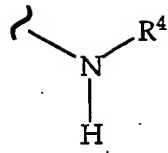
159

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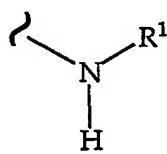
160



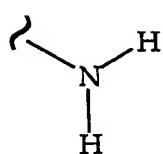
161



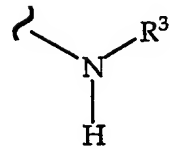
162



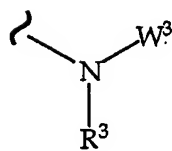
163



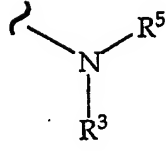
164



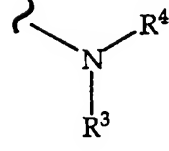
165



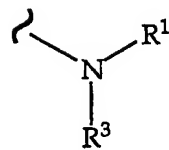
166



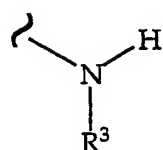
167



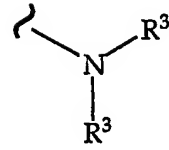
168



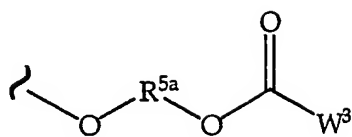
169



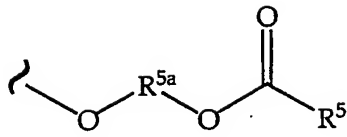
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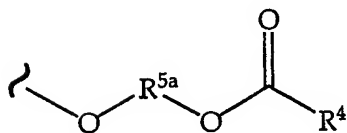
171

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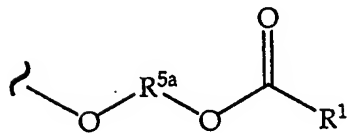
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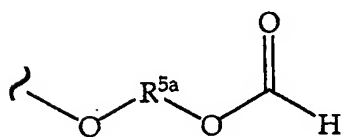
173



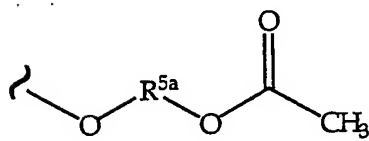
174



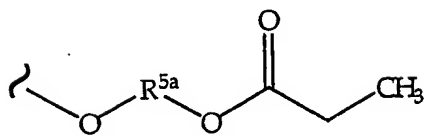
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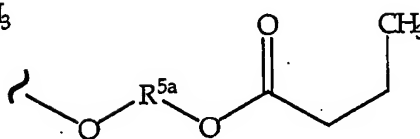
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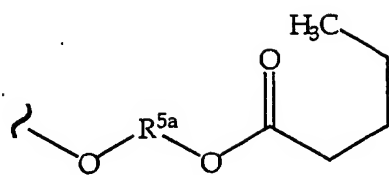
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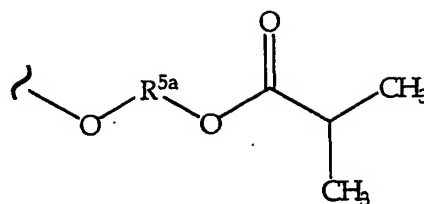
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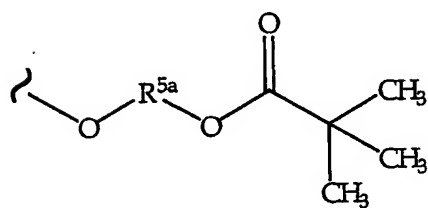
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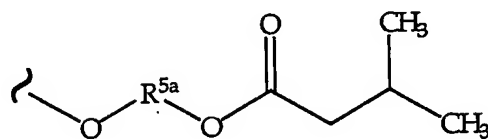
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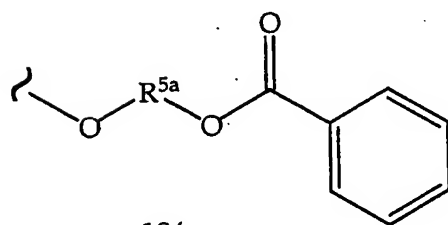
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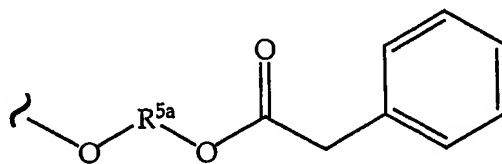
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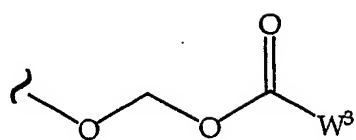
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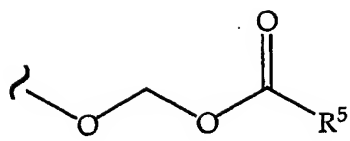
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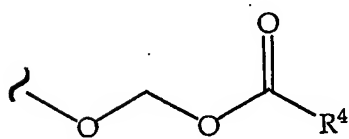
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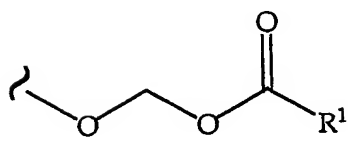
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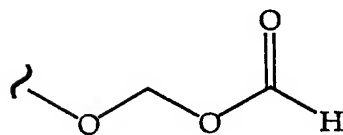
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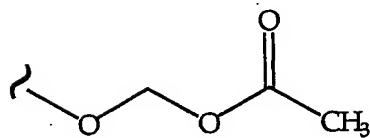
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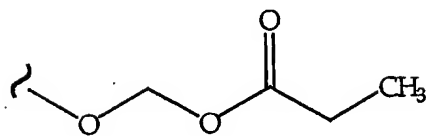
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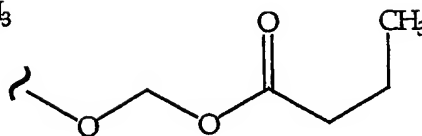
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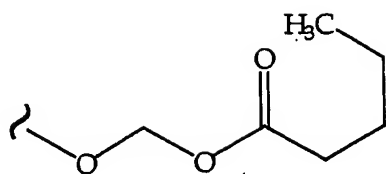


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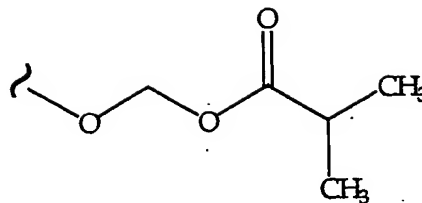


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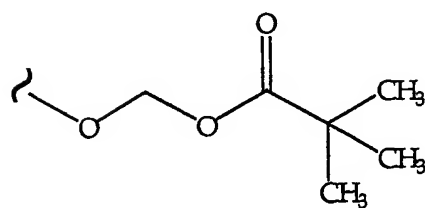
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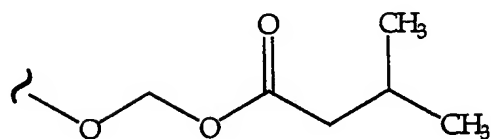
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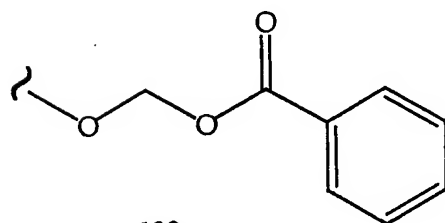
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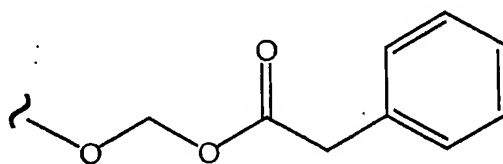
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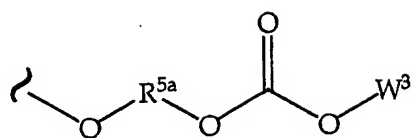


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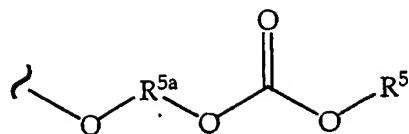


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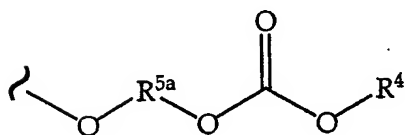
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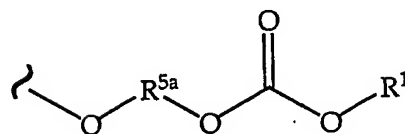
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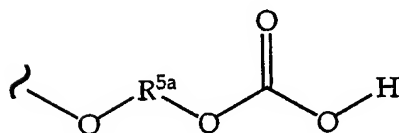
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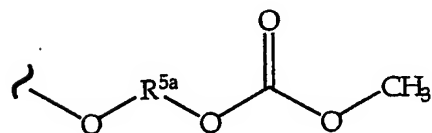
202



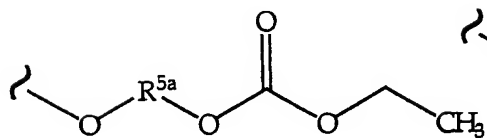
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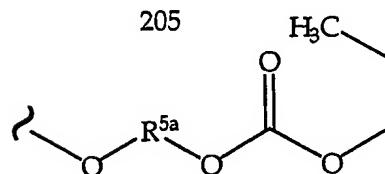
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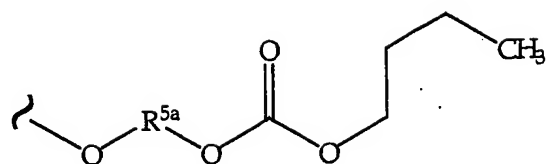


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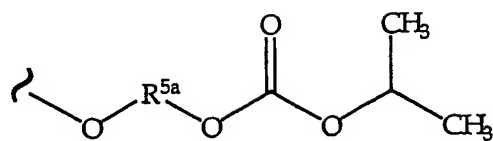


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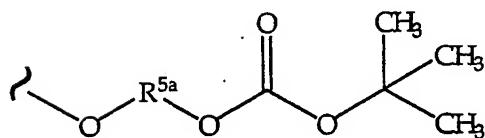
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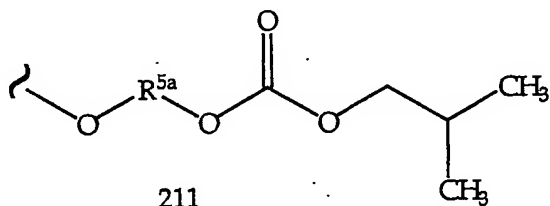
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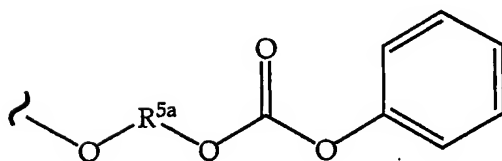
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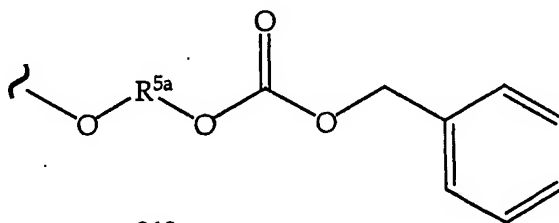
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211

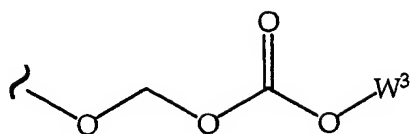


212

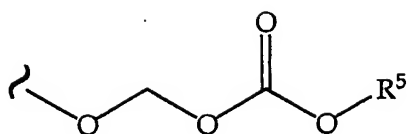


213

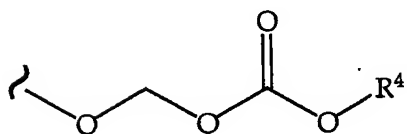
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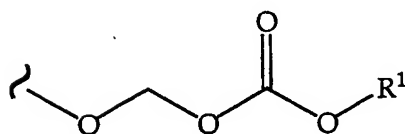
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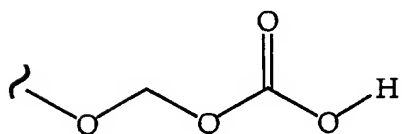
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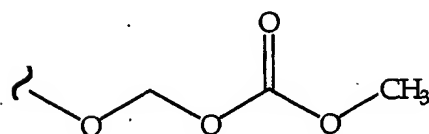
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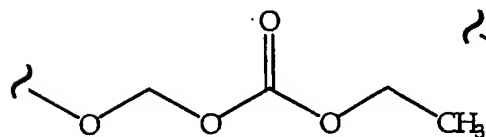
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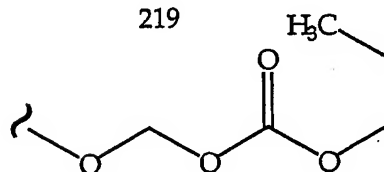
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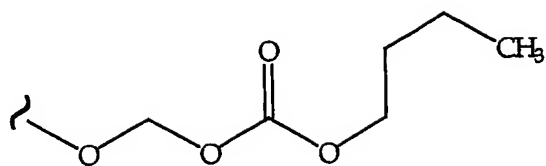
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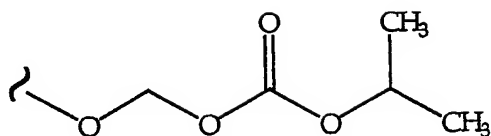
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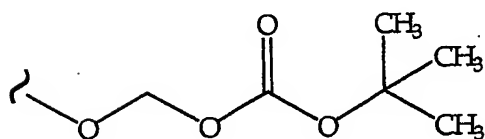
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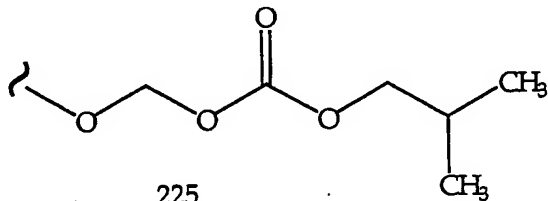
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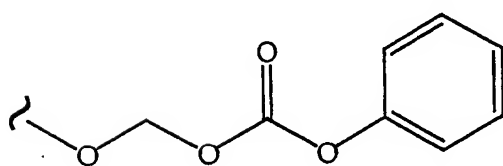
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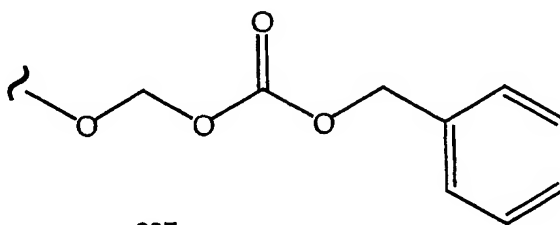
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225



226



227

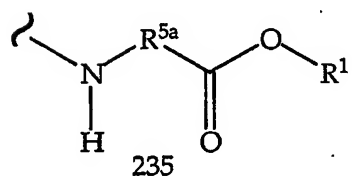
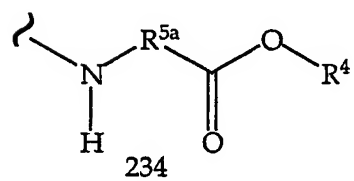
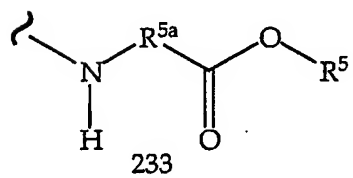
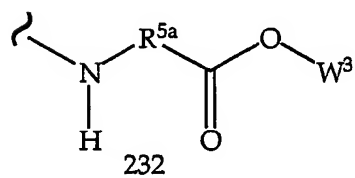
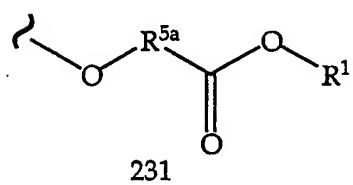
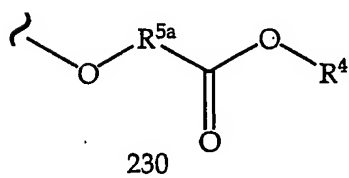
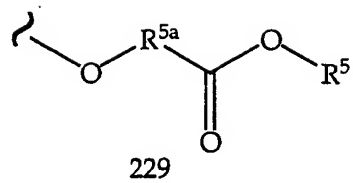
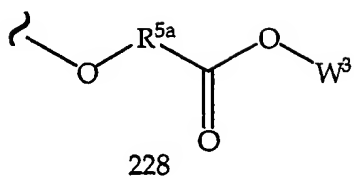
Table 20.32

Table 20.36

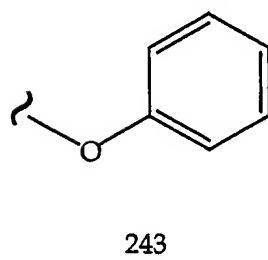
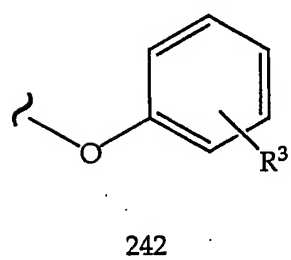
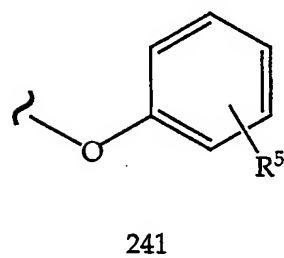
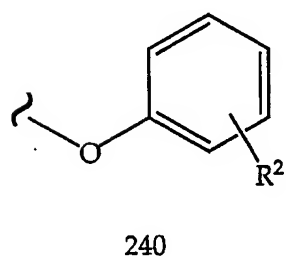
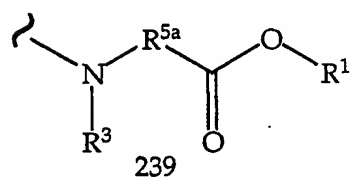
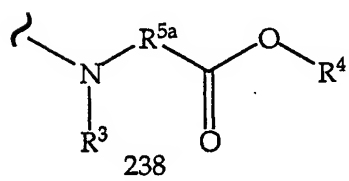
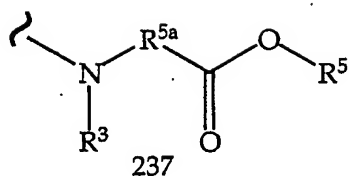
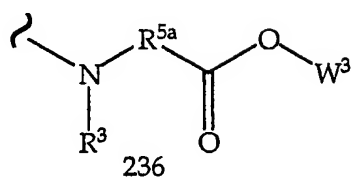


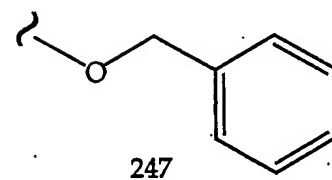
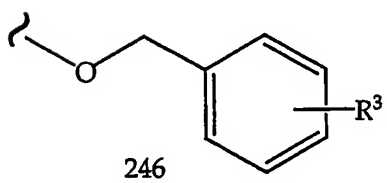
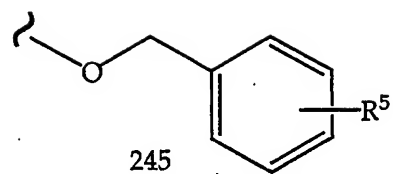
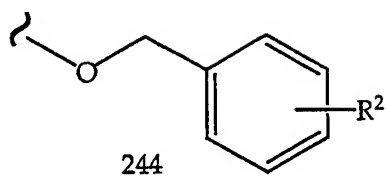
Table 20.37

Table 100

Prodrugs of 1.B

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- 30 1.B.157.169; 1.B.157.172; 1.B.157.175; 1.B.157.240; 1.B.157.244; 1.B.166.228;
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- 1.B.166.239; 1.B.166.154; 1.B.166.157; 1.B.166.166; 1.B.166.169; 1.B.166.172;
 1.B.166.175; 1.B.166.240; 1.B.166.244; 1.B.169.228; 1.B.169.229; 1.B.169.230;
 1.B.169.231; 1.B.169.236; 1.B.169.237; 1.B.169.238; 1.B.169.239; 1.B.169.154;
 1.B.169.157; 1.B.169.166; 1.B.169.169; 1.B.169.172; 1.B.169.175; 1.B.169.240;
 5 1.B.169.244; 1.B.172.228; 1.B.172.229; 1.B.172.230; 1.B.172.231; 1.B.172.236;
 1.B.172.237; 1.B.172.238; 1.B.172.239; 1.B.172.154; 1.B.172.157; 1.B.172.166;
 1.B.172.169; 1.B.172.172; 1.B.172.175; 1.B.172.240; 1.B.172.244; 1.B.175.228;
 1.B.175.229; 1.B.175.230; 1.B.175.231; 1.B.175.236; 1.B.175.237; 1.B.175.238;
 1.B.175.239; 1.B.175.154; 1.B.175.157; 1.B.175.166; 1.B.175.169; 1.B.175.172;
 10 1.B.175.175; 1.B.175.240; 1.B.175.244; 1.B.240.228; 1.B.240.229; 1.B.240.230;
 1.B.240.231; 1.B.240.236; 1.B.240.237; 1.B.240.238; 1.B.240.239; 1.B.240.154;
 1.B.240.157; 1.B.240.166; 1.B.240.169; 1.B.240.172; 1.B.240.175; 1.B.240.240;
 1.B.240.244; 1.B.244.228; 1.B.244.229; 1.B.244.230; 1.B.244.231; 1.B.244.236;
 1.B.244.237; 1.B.244.238; 1.B.244.239; 1.B.244.154; 1.B.244.157; 1.B.244.166;
 15 1.B.244.169; 1.B.244.172; 1.B.244.175; 1.B.244.240; 1.B.244.244;

Prodrugs of 1.D

- 1.D.228.228; 1.D.228.229; 1.D.228.230; 1.D.228.231; 1.D.228.236;
 1.D.228.237; 1.D.228.238; 1.D.228.239; 1.D.228.154; 1.D.228.157;
 20 1.D.228.166; 1.D.228.169; 1.D.228.172; 1.D.228.175; 1.D.228.240;
 1.D.228.244; 1.D.229.228; 1.D.229.229; 1.D.229.230; 1.D.229.231;
 1.D.229.236; 1.D.229.237; 1.D.229.238; 1.D.229.239; 1.D.229.154;
 1.D.229.157; 1.D.229.166; 1.D.229.169; 1.D.229.172; 1.D.229.175;
 1.D.229.240; 1.D.229.244; 1.D.230.228; 1.D.230.229; 1.D.230.230;
 25 1.D.230.231; 1.D.230.236; 1.D.230.237; 1.D.230.238; 1.D.230.239;
 1.D.230.154; 1.D.230.157; 1.D.230.166; 1.D.230.169; 1.D.230.172;
 1.D.230.175; 1.D.230.240; 1.D.230.244; 1.D.231.228; 1.D.231.229;
 1.D.231.230; 1.D.231.231; 1.D.231.236; 1.D.231.237; 1.D.231.238;
 1.D.231.239; 1.D.231.154; 1.D.231.157; 1.D.231.166; 1.D.231.169;
 30 1.D.231.172; 1.D.231.175; 1.D.231.240; 1.D.231.244; 1.D.236.228;
 1.D.236.229; 1.D.236.230; 1.D.236.231; 1.D.236.236; 1.D.236.237;

1.D.236.238; 1.D.236.239; 1.D.236.154; 1.D.236.157; 1.D.236.166;
1.D.236.169; 1.D.236.172; 1.D.236.175; 1.D.236.240; 1.D.236.244;
1.D.237.228; 1.D.237.229; 1.D.237.230; 1.D.237.231; 1.D.237.236;
1.D.237.237; 1.D.237.238; 1.D.237.239; 1.D.237.154; 1.D.237.157;
5 1.D.237.166; 1.D.237.169; 1.D.237.172; 1.D.237.175; 1.D.237.240;
1.D.237.244; 1.D.238.228; 1.D.238.229; 1.D.238.230; 1.D.238.231;
1.D.238.236; 1.D.238.237; 1.D.238.238; 1.D.238.239; 1.D.238.154;
1.D.238.157; 1.D.238.166; 1.D.238.169; 1.D.238.172; 1.D.238.175;
1.D.238.240; 1.D.238.244; 1.D.239.228; 1.D.239.229; 1.D.239.230;
10 1.D.239.231; 1.D.239.236; 1.D.239.237; 1.D.239.238; 1.D.239.239;
1.D.239.154; 1.D.239.157; 1.D.239.166; 1.D.239.169; 1.D.239.172;
1.D.239.175; 1.D.239.240; 1.D.239.244; 1.D.154.228; 1.D.154.229;
1.D.154.230; 1.D.154.231; 1.D.154.236; 1.D.154.237; 1.D.154.238;
1.D.154.239; 1.D.154.154; 1.D.154.157; 1.D.154.166; 1.D.154.169;
15 1.D.154.172; 1.D.154.175; 1.D.154.240; 1.D.154.244; 1.D.157.228;
1.D.157.229; 1.D.157.230; 1.D.157.231; 1.D.157.236; 1.D.157.237;
1.D.157.238; 1.D.157.239; 1.D.157.154; 1.D.157.157; 1.D.157.166;
1.D.157.169; 1.D.157.172; 1.D.157.175; 1.D.157.240; 1.D.157.244;
1.D.166.228; 1.D.166.229; 1.D.166.230; 1.D.166.231; 1.D.166.236;
20 1.D.166.237; 1.D.166.238; 1.D.166.239; 1.D.166.154; 1.D.166.157;
1.D.166.166; 1.D.166.169; 1.D.166.172; 1.D.166.175; 1.D.166.240;
1.D.166.244; 1.D.169.228; 1.D.169.229; 1.D.169.230; 1.D.169.231;
1.D.169.236; 1.D.169.237; 1.D.169.238; 1.D.169.239; 1.D.169.154;
1.D.169.157; 1.D.169.166; 1.D.169.169; 1.D.169.172; 1.D.169.175;
25 1.D.169.240; 1.D.169.244; 1.D.172.228; 1.D.172.229; 1.D.172.230;
1.D.172.231; 1.D.172.236; 1.D.172.237; 1.D.172.238; 1.D.172.239;
1.D.172.154; 1.D.172.157; 1.D.172.166; 1.D.172.169; 1.D.172.172;
1.D.172.175; 1.D.172.240; 1.D.172.244; 1.D.175.228; 1.D.175.229;
1.D.175.230; 1.D.175.231; 1.D.175.236; 1.D.175.237; 1.D.175.238;
30 1.D.175.239; 1.D.175.154; 1.D.175.157; 1.D.175.166; 1.D.175.169;
1.D.175.172; 1.D.175.175; 1.D.175.240; 1.D.175.244; 1.D.240.228;

1.D.240.229; 1.D.240.230; 1.D.240.231; 1.D.240.236; 1.D.240.237;
 1.D.240.238; 1.D.240.239; 1.D.240.154; 1.D.240.157; 1.D.240.166;
 1.D.240.169; 1.D.240.172; 1.D.240.175; 1.D.240.240; 1.D.240.244;
 1.D.244.228; 1.D.244.229; 1.D.244.230; 1.D.244.231; 1.D.244.236;
 5 1.D.244.237; 1.D.244.238; 1.D.244.239; 1.D.244.154; 1.D.244.157;
 1.D.244.166; 1.D.244.169; 1.D.244.172; 1.D.244.175; 1.D.244.240;
 1.D.244.244;

Prodrugs of 1.E

10 1.E.228.228; 1.E.228.229; 1.E.228.230; 1.E.228.231; 1.E.228.236;
 1.E.228.237; 1.E.228.238; 1.E.228.239; 1.E.228.154; 1.E.228.157; 1.E.228.166;
 1.E.228.169; 1.E.228.172; 1.E.228.175; 1.E.228.240; 1.E.228.244; 1.E.229.228;
 1.E.229.229; 1.E.229.230; 1.E.229.231; 1.E.229.236; 1.E.229.237; 1.E.229.238;
 1.E.229.239; 1.E.229.154; 1.E.229.157; 1.E.229.166; 1.E.229.169; 1.E.229.172;
 15 1.E.229.175; 1.E.229.240; 1.E.229.244; 1.E.230.228; 1.E.230.229; 1.E.230.230;
 1.E.230.231; 1.E.230.236; 1.E.230.237; 1.E.230.238; 1.E.230.239; 1.E.230.154;
 1.E.230.157; 1.E.230.166; 1.E.230.169; 1.E.230.172; 1.E.230.175; 1.E.230.240;
 1.E.230.244; 1.E.231.228; 1.E.231.229; 1.E.231.230; 1.E.231.231; 1.E.231.236;
 1.E.231.237; 1.E.231.238; 1.E.231.239; 1.E.231.154; 1.E.231.157; 1.E.231.166;
 20 1.E.231.169; 1.E.231.172; 1.E.231.175; 1.E.231.240; 1.E.231.244; 1.E.236.228;
 1.E.236.229; 1.E.236.230; 1.E.236.231; 1.E.236.236; 1.E.236.237; 1.E.236.238;
 1.E.236.239; 1.E.236.154; 1.E.236.157; 1.E.236.166; 1.E.236.169; 1.E.236.172;
 1.E.236.175; 1.E.236.240; 1.E.236.244; 1.E.237.228; 1.E.237.229; 1.E.237.230;
 1.E.237.231; 1.E.237.236; 1.E.237.237; 1.E.237.238; 1.E.237.239; 1.E.237.154;
 25 1.E.237.157; 1.E.237.166; 1.E.237.169; 1.E.237.172; 1.E.237.175; 1.E.237.240;
 1.E.237.244; 1.E.238.228; 1.E.238.229; 1.E.238.230; 1.E.238.231; 1.E.238.236;
 1.E.238.237; 1.E.238.238; 1.E.238.239; 1.E.238.154; 1.E.238.157; 1.E.238.166;
 1.E.238.169; 1.E.238.172; 1.E.238.175; 1.E.238.240; 1.E.238.244; 1.E.239.228;
 1.E.239.229; 1.E.239.230; 1.E.239.231; 1.E.239.236; 1.E.239.237; 1.E.239.238;
 30 1.E.239.239; 1.E.239.154; 1.E.239.157; 1.E.239.166; 1.E.239.169; 1.E.239.172;
 1.E.239.175; 1.E.239.240; 1.E.239.244; 1.E.154.228; 1.E.154.229; 1.E.154.230;

1.E.154.231; 1.E.154.236; 1.E.154.237; 1.E.154.238; 1.E.154.239; 1.E.154.154;
 1.E.154.157; 1.E.154.166; 1.E.154.169; 1.E.154.172; 1.E.154.175; 1.E.154.240;
 1.E.154.244; 1.E.157.228; 1.E.157.229; 1.E.157.230; 1.E.157.231; 1.E.157.236;
 1.E.157.237; 1.E.157.238; 1.E.157.239; 1.E.157.154; 1.E.157.157; 1.E.157.166;
 5 1.E.157.169; 1.E.157.172; 1.E.157.175; 1.E.157.240; 1.E.157.244; 1.E.166.228;
 1.E.166.229; 1.E.166.230; 1.E.166.231; 1.E.166.236; 1.E.166.237; 1.E.166.238;
 1.E.166.239; 1.E.166.154; 1.E.166.157; 1.E.166.166; 1.E.166.169; 1.E.166.172;
 1.E.166.175; 1.E.166.240; 1.E.166.244; 1.E.169.228; 1.E.169.229; 1.E.169.230;
 1.E.169.231; 1.E.169.236; 1.E.169.237; 1.E.169.238; 1.E.169.239; 1.E.169.154;
 10 1.E.169.157; 1.E.169.166; 1.E.169.169; 1.E.169.172; 1.E.169.175; 1.E.169.240;
 1.E.169.244; 1.E.172.228; 1.E.172.229; 1.E.172.230; 1.E.172.231; 1.E.172.236;
 1.E.172.237; 1.E.172.238; 1.E.172.239; 1.E.172.154; 1.E.172.157; 1.E.172.166;
 1.E.172.169; 1.E.172.172; 1.E.172.175; 1.E.172.240; 1.E.172.244; 1.E.175.228;
 1.E.175.229; 1.E.175.230; 1.E.175.231; 1.E.175.236; 1.E.175.237; 1.E.175.238;
 15 1.E.175.239; 1.E.175.154; 1.E.175.157; 1.E.175.166; 1.E.175.169; 1.E.175.172;
 1.E.175.175; 1.E.175.240; 1.E.175.244; 1.E.240.228; 1.E.240.229; 1.E.240.230;
 1.E.240.231; 1.E.240.236; 1.E.240.237; 1.E.240.238; 1.E.240.239; 1.E.240.154;
 1.E.240.157; 1.E.240.166; 1.E.240.169; 1.E.240.172; 1.E.240.175; 1.E.240.240;
 1.E.240.244; 1.E.244.228; 1.E.244.229; 1.E.244.230; 1.E.244.231; 1.E.244.236;
 20 1.E.244.237; 1.E.244.238; 1.E.244.239; 1.E.244.154; 1.E.244.157; 1.E.244.166;
 1.E.244.169; 1.E.244.172; 1.E.244.175; 1.E.244.240; 1.E.244.244;

Prodrugs of 1.G

1.G.228.228; 1.G.228.229; 1.G.228.230; 1.G.228.231; 1.G.228.236;
 25 1.G.228.237; 1.G.228.238; 1.G.228.239; 1.G.228.154; 1.G.228.157;
 1.G.228.166; 1.G.228.169; 1.G.228.172; 1.G.228.175; 1.G.228.240;
 1.G.228.244; 1.G.229.228; 1.G.229.229; 1.G.229.230; 1.G.229.231;
 1.G.229.236; 1.G.229.237; 1.G.229.238; 1.G.229.239; 1.G.229.154;
 1.G.229.157; 1.G.229.166; 1.G.229.169; 1.G.229.172; 1.G.229.175;
 30 1.G.229.240; 1.G.229.244; 1.G.230.228; 1.G.230.229; 1.G.230.230;
 1.G.230.231; 1.G.230.236; 1.G.230.237; 1.G.230.238; 1.G.230.239;

- 1.G.230.154; 1.G.230.157; 1.G.230.166; 1.G.230.169; 1.G.230.172;
1.G.230.175; 1.G.230.240; 1.G.230.244; 1.G.231.228; 1.G.231.229;
1.G.231.230; 1.G.231.231; 1.G.231.236; 1.G.231.237; 1.G.231.238;
1.G.231.239; 1.G.231.154; 1.G.231.157; 1.G.231.166; 1.G.231.169;
5 1.G.231.172; 1.G.231.175; 1.G.231.240; 1.G.231.244; 1.G.236.228;
1.G.236.229; 1.G.236.230; 1.G.236.231; 1.G.236.236; 1.G.236.237;
1.G.236.238; 1.G.236.239; 1.G.236.154; 1.G.236.157; 1.G.236.166;
1.G.236.169; 1.G.236.172; 1.G.236.175; 1.G.236.240; 1.G.236.244;
1.G.237.228; 1.G.237.229; 1.G.237.230; 1.G.237.231; 1.G.237.236;
10 1.G.237.237; 1.G.237.238; 1.G.237.239; 1.G.237.154; 1.G.237.157;
1.G.237.166; 1.G.237.169; 1.G.237.172; 1.G.237.175; 1.G.237.240;
1.G.237.244; 1.G.238.228; 1.G.238.229; 1.G.238.230; 1.G.238.231;
1.G.238.236; 1.G.238.237; 1.G.238.238; 1.G.238.239; 1.G.238.154;
1.G.238.157; 1.G.238.166; 1.G.238.169; 1.G.238.172; 1.G.238.175;
15 1.G.238.240; 1.G.238.244; 1.G.239.228; 1.G.239.229; 1.G.239.230;
1.G.239.231; 1.G.239.236; 1.G.239.237; 1.G.239.238; 1.G.239.239;
1.G.239.154; 1.G.239.157; 1.G.239.166; 1.G.239.169; 1.G.239.172;
1.G.239.175; 1.G.239.240; 1.G.239.244; 1.G.154.228; 1.G.154.229;
1.G.154.230; 1.G.154.231; 1.G.154.236; 1.G.154.237; 1.G.154.238;
20 1.G.154.239; 1.G.154.154; 1.G.154.157; 1.G.154.166; 1.G.154.169;
1.G.154.172; 1.G.154.175; 1.G.154.240; 1.G.154.244; 1.G.157.228;
1.G.157.229; 1.G.157.230; 1.G.157.231; 1.G.157.236; 1.G.157.237;
1.G.157.238; 1.G.157.239; 1.G.157.154; 1.G.157.157; 1.G.157.166;
1.G.157.169; 1.G.157.172; 1.G.157.175; 1.G.157.240; 1.G.157.244;
25 1.G.166.228; 1.G.166.229; 1.G.166.230; 1.G.166.231; 1.G.166.236;
1.G.166.237; 1.G.166.238; 1.G.166.239; 1.G.166.154; 1.G.166.157;
1.G.166.166; 1.G.166.169; 1.G.166.172; 1.G.166.175; 1.G.166.240;
1.G.166.244; 1.G.169.228; 1.G.169.229; 1.G.169.230; 1.G.169.231;
1.G.169.236; 1.G.169.237; 1.G.169.238; 1.G.169.239; 1.G.169.154;
30 1.G.169.157; 1.G.169.166; 1.G.169.169; 1.G.169.172; 1.G.169.175;
1.G.169.240; 1.G.169.244; 1.G.172.228; 1.G.172.229; 1.G.172.230;

- 1.G.172.231; 1.G.172.236; 1.G.172.237; 1.G.172.238; 1.G.172.239;
 1.G.172.154; 1.G.172.157; 1.G.172.166; 1.G.172.169; 1.G.172.172;
 1.G.172.175; 1.G.172.240; 1.G.172.244; 1.G.175.228; 1.G.175.229;
 1.G.175.230; 1.G.175.231; 1.G.175.236; 1.G.175.237; 1.G.175.238;
 5 1.G.175.239; 1.G.175.154; 1.G.175.157; 1.G.175.166; 1.G.175.169;
 1.G.175.172; 1.G.175.175; 1.G.175.240; 1.G.175.244; 1.G.240.228;
 1.G.240.229; 1.G.240.230; 1.G.240.231; 1.G.240.236; 1.G.240.237;
 1.G.240.238; 1.G.240.239; 1.G.240.154; 1.G.240.157; 1.G.240.166;
 1.G.240.169; 1.G.240.172; 1.G.240.175; 1.G.240.240; 1.G.240.244;
 10 1.G.244.228; 1.G.244.229; 1.G.244.230; 1.G.244.231; 1.G.244.236;
 1.G.244.237; 1.G.244.238; 1.G.244.239; 1.G.244.154; 1.G.244.157;
 1.G.244.166; 1.G.244.169; 1.G.244.172; 1.G.244.175; 1.G.244.240;
 1.G.244.244;
- 15 Prodrugs of 1.I
 1.I.228.228; 1.I.228.229; 1.I.228.230; 1.I.228.231; 1.I.228.236; 1.I.228.237;
 1.I.228.238; 1.I.228.239; 1.I.228.154; 1.I.228.157; 1.I.228.166; 1.I.228.169;
 1.I.228.172; 1.I.228.175; 1.I.228.240; 1.I.228.244; 1.I.229.228; 1.I.229.229;
 1.I.229.230; 1.I.229.231; 1.I.229.236; 1.I.229.237; 1.I.229.238; 1.I.229.239;
 20 1.I.229.154; 1.I.229.157; 1.I.229.166; 1.I.229.169; 1.I.229.172; 1.I.229.175;
 1.I.229.240; 1.I.229.244; 1.I.230.228; 1.I.230.229; 1.I.230.230; 1.I.230.231;
 1.I.230.236; 1.I.230.237; 1.I.230.238; 1.I.230.239; 1.I.230.154; 1.I.230.157;
 1.I.230.166; 1.I.230.169; 1.I.230.172; 1.I.230.175; 1.I.230.240; 1.I.230.244;
 1.I.231.228; 1.I.231.229; 1.I.231.230; 1.I.231.231; 1.I.231.236; 1.I.231.237;
 25 1.I.231.238; 1.I.231.239; 1.I.231.154; 1.I.231.157; 1.I.231.166; 1.I.231.169;
 1.I.231.172; 1.I.231.175; 1.I.231.240; 1.I.231.244; 1.I.236.228; 1.I.236.229;
 1.I.236.230; 1.I.236.231; 1.I.236.236; 1.I.236.237; 1.I.236.238; 1.I.236.239;
 1.I.236.154; 1.I.236.157; 1.I.236.166; 1.I.236.169; 1.I.236.172; 1.I.236.175;
 1.I.236.240; 1.I.236.244; 1.I.237.228; 1.I.237.229; 1.I.237.230; 1.I.237.231;
 30 1.I.237.236; 1.I.237.237; 1.I.237.238; 1.I.237.239; 1.I.237.154; 1.I.237.157;
 1.I.237.166; 1.I.237.169; 1.I.237.172; 1.I.237.175; 1.I.237.240; 1.I.237.244;

1.I.238.228; 1.I.238.229; 1.I.238.230; 1.I.238.231; 1.I.238.236; 1.I.238.237;
 1.I.238.238; 1.I.238.239; 1.I.238.154; 1.I.238.157; 1.I.238.166; 1.I.238.169;
 1.I.238.172; 1.I.238.175; 1.I.238.240; 1.I.238.244; 1.I.239.228; 1.I.239.229;
 1.I.239.230; 1.I.239.231; 1.I.239.236; 1.I.239.237; 1.I.239.238; 1.I.239.239;
 5 1.I.239.154; 1.I.239.157; 1.I.239.166; 1.I.239.169; 1.I.239.172; 1.I.239.175;
 1.I.239.240; 1.I.239.244; 1.I.154.228; 1.I.154.229; 1.I.154.230; 1.I.154.231;
 1.I.154.236; 1.I.154.237; 1.I.154.238; 1.I.154.239; 1.I.154.154; 1.I.154.157;
 1.I.154.166; 1.I.154.169; 1.I.154.172; 1.I.154.175; 1.I.154.240; 1.I.154.244;
 1.I.157.228; 1.I.157.229; 1.I.157.230; 1.I.157.231; 1.I.157.236; 1.I.157.237;
 10 1.I.157.238; 1.I.157.239; 1.I.157.154; 1.I.157.157; 1.I.157.166; 1.I.157.169;
 1.I.157.172; 1.I.157.175; 1.I.157.240; 1.I.157.244; 1.I.166.228; 1.I.166.229;
 1.I.166.230; 1.I.166.231; 1.I.166.236; 1.I.166.237; 1.I.166.238; 1.I.166.239;
 1.I.166.154; 1.I.166.157; 1.I.166.166; 1.I.166.169; 1.I.166.172; 1.I.166.175;
 1.I.166.240; 1.I.166.244; 1.I.169.228; 1.I.169.229; 1.I.169.230; 1.I.169.231;
 15 1.I.169.236; 1.I.169.237; 1.I.169.238; 1.I.169.239; 1.I.169.154; 1.I.169.157;
 1.I.169.166; 1.I.169.169; 1.I.169.172; 1.I.169.175; 1.I.169.240; 1.I.169.244;
 1.I.172.228; 1.I.172.229; 1.I.172.230; 1.I.172.231; 1.I.172.236; 1.I.172.237;
 1.I.172.238; 1.I.172.239; 1.I.172.154; 1.I.172.157; 1.I.172.166; 1.I.172.169;
 1.I.172.172; 1.I.172.175; 1.I.172.240; 1.I.172.244; 1.I.175.228; 1.I.175.229;
 20 1.I.175.230; 1.I.175.231; 1.I.175.236; 1.I.175.237; 1.I.175.238; 1.I.175.239;
 1.I.175.154; 1.I.175.157; 1.I.175.166; 1.I.175.169; 1.I.175.172; 1.I.175.175;
 1.I.175.240; 1.I.175.244; 1.I.240.228; 1.I.240.229; 1.I.240.230; 1.I.240.231;
 1.I.240.236; 1.I.240.237; 1.I.240.238; 1.I.240.239; 1.I.240.154; 1.I.240.157;
 1.I.240.166; 1.I.240.169; 1.I.240.172; 1.I.240.175; 1.I.240.240; 1.I.240.244;
 25 1.I.244.228; 1.I.244.229; 1.I.244.230; 1.I.244.231; 1.I.244.236; 1.I.244.237;
 1.I.244.238; 1.I.244.239; 1.I.244.154; 1.I.244.157; 1.I.244.166; 1.I.244.169;
 1.I.244.172; 1.I.244.175; 1.I.244.240; 1.I.244.244;

Prodrugs of 1.I

30 1.J.228.228; 1.J.228.229; 1.J.228.230; 1.J.228.231; 1.J.228.236; 1.J.228.237;
 1.J.228.238; 1.J.228.239; 1.J.228.154; 1.J.228.157; 1.J.228.166; 1.J.228.169;

- 1.J.228.172; 1.J.228.175; 1.J.228.240; 1.J.228.244; 1.J.229.228; 1.J.229.229;
1.J.229.230; 1.J.229.231; 1.J.229.236; 1.J.229.237; 1.J.229.238; 1.J.229.239;
1.J.229.154; 1.J.229.157; 1.J.229.166; 1.J.229.169; 1.J.229.172; 1.J.229.175;
1.J.229.240; 1.J.229.244; 1.J.230.228; 1.J.230.229; 1.J.230.230; 1.J.230.231;
5 1.J.230.236; 1.J.230.237; 1.J.230.238; 1.J.230.239; 1.J.230.154; 1.J.230.157;
1.J.230.166; 1.J.230.169; 1.J.230.172; 1.J.230.175; 1.J.230.240; 1.J.230.244;
1.J.231.228; 1.J.231.229; 1.J.231.230; 1.J.231.231; 1.J.231.236; 1.J.231.237;
1.J.231.238; 1.J.231.239; 1.J.231.154; 1.J.231.157; 1.J.231.166; 1.J.231.169;
1.J.231.172; 1.J.231.175; 1.J.231.240; 1.J.231.244; 1.J.236.228; 1.J.236.229;
10 1.J.236.230; 1.J.236.231; 1.J.236.236; 1.J.236.237; 1.J.236.238; 1.J.236.239;
1.J.236.154; 1.J.236.157; 1.J.236.166; 1.J.236.169; 1.J.236.172; 1.J.236.175;
1.J.236.240; 1.J.236.244; 1.J.237.228; 1.J.237.229; 1.J.237.230; 1.J.237.231;
1.J.237.236; 1.J.237.237; 1.J.237.238; 1.J.237.239; 1.J.237.154; 1.J.237.157;
1.J.237.166; 1.J.237.169; 1.J.237.172; 1.J.237.175; 1.J.237.240; 1.J.237.244;
15 1.J.238.228; 1.J.238.229; 1.J.238.230; 1.J.238.231; 1.J.238.236; 1.J.238.237;
1.J.238.238; 1.J.238.239; 1.J.238.154; 1.J.238.157; 1.J.238.166; 1.J.238.169;
1.J.238.172; 1.J.238.175; 1.J.238.240; 1.J.238.244; 1.J.239.228; 1.J.239.229;
1.J.239.230; 1.J.239.231; 1.J.239.236; 1.J.239.237; 1.J.239.238; 1.J.239.239;
1.J.239.154; 1.J.239.157; 1.J.239.166; 1.J.239.169; 1.J.239.172; 1.J.239.175;
20 1.J.239.240; 1.J.239.244; 1.J.154.228; 1.J.154.229; 1.J.154.230; 1.J.154.231;
1.J.154.236; 1.J.154.237; 1.J.154.238; 1.J.154.239; 1.J.154.154; 1.J.154.157;
1.J.154.166; 1.J.154.169; 1.J.154.172; 1.J.154.175; 1.J.154.240; 1.J.154.244;
1.J.157.228; 1.J.157.229; 1.J.157.230; 1.J.157.231; 1.J.157.236; 1.J.157.237;
1.J.157.238; 1.J.157.239; 1.J.157.154; 1.J.157.157; 1.J.157.166; 1.J.157.169;
25 1.J.157.172; 1.J.157.175; 1.J.157.240; 1.J.157.244; 1.J.166.228; 1.J.166.229;
1.J.166.230; 1.J.166.231; 1.J.166.236; 1.J.166.237; 1.J.166.238; 1.J.166.239;
1.J.166.154; 1.J.166.157; 1.J.166.166; 1.J.166.169; 1.J.166.172; 1.J.166.175;
1.J.166.240; 1.J.166.244; 1.J.169.228; 1.J.169.229; 1.J.169.230; 1.J.169.231;
1.J.169.236; 1.J.169.237; 1.J.169.238; 1.J.169.239; 1.J.169.154; 1.J.169.157;
30 1.J.169.166; 1.J.169.169; 1.J.169.172; 1.J.169.175; 1.J.169.240; 1.J.169.244;
1.J.172.228; 1.J.172.229; 1.J.172.230; 1.J.172.231; 1.J.172.236; 1.J.172.237;

1.J.172.238; 1.J.172.239; 1.J.172.154; 1.J.172.157; 1.J.172.166; 1.J.172.169;
 1.J.172.172; 1.J.172.175; 1.J.172.240; 1.J.172.244; 1.J.175.228; 1.J.175.229;
 1.J.175.230; 1.J.175.231; 1.J.175.236; 1.J.175.237; 1.J.175.238; 1.J.175.239;
 1.J.175.154; 1.J.175.157; 1.J.175.166; 1.J.175.169; 1.J.175.172; 1.J.175.175;
 5 1.J.175.240; 1.J.175.244; 1.J.240.228; 1.J.240.229; 1.J.240.230; 1.J.240.231;
 1.J.240.236; 1.J.240.237; 1.J.240.238; 1.J.240.239; 1.J.240.154; 1.J.240.157;
 1.J.240.166; 1.J.240.169; 1.J.240.172; 1.J.240.175; 1.J.240.240; 1.J.240.244;
 1.J.244.228; 1.J.244.229; 1.J.244.230; 1.J.244.231; 1.J.244.236; 1.J.244.237;
 1.J.244.238; 1.J.244.239; 1.J.244.154; 1.J.244.157; 1.J.244.166; 1.J.244.169;
 10 1.J.244.172; 1.J.244.175; 1.J.244.240; 1.J.244.244;

Prodrugs of 1.L

1.L.228.228; 1.L.228.229; 1.L.228.230; 1.L.228.231; 1.L.228.236;
 1.L.228.237; 1.L.228.238; 1.L.228.239; 1.L.228.154; 1.L.228.157; 1.L.228.166;
 15 1.L.228.169; 1.L.228.172; 1.L.228.175; 1.L.228.240; 1.L.228.244; 1.L.229.228;
 1.L.229.229; 1.L.229.230; 1.L.229.231; 1.L.229.236; 1.L.229.237; 1.L.229.238;
 1.L.229.239; 1.L.229.154; 1.L.229.157; 1.L.229.166; 1.L.229.169; 1.L.229.172;
 1.L.229.175; 1.L.229.240; 1.L.229.244; 1.L.230.228; 1.L.230.229; 1.L.230.230;
 1.L.230.231; 1.L.230.236; 1.L.230.237; 1.L.230.238; 1.L.230.239; 1.L.230.154;
 20 1.L.230.157; 1.L.230.166; 1.L.230.169; 1.L.230.172; 1.L.230.175; 1.L.230.240;
 1.L.230.244; 1.L.231.228; 1.L.231.229; 1.L.231.230; 1.L.231.231; 1.L.231.236;
 1.L.231.237; 1.L.231.238; 1.L.231.239; 1.L.231.154; 1.L.231.157; 1.L.231.166;
 1.L.231.169; 1.L.231.172; 1.L.231.175; 1.L.231.240; 1.L.231.244; 1.L.236.228;
 1.L.236.229; 1.L.236.230; 1.L.236.231; 1.L.236.236; 1.L.236.237; 1.L.236.238;
 25 1.L.236.239; 1.L.236.154; 1.L.236.157; 1.L.236.166; 1.L.236.169; 1.L.236.172;
 1.L.236.175; 1.L.236.240; 1.L.236.244; 1.L.237.228; 1.L.237.229; 1.L.237.230;
 1.L.237.231; 1.L.237.236; 1.L.237.237; 1.L.237.238; 1.L.237.239; 1.L.237.154;
 1.L.237.157; 1.L.237.166; 1.L.237.169; 1.L.237.172; 1.L.237.175; 1.L.237.240;
 1.L.237.244; 1.L.238.228; 1.L.238.229; 1.L.238.230; 1.L.238.231; 1.L.238.236;
 30 1.L.238.237; 1.L.238.238; 1.L.238.239; 1.L.238.154; 1.L.238.157; 1.L.238.166;
 1.L.238.169; 1.L.238.172; 1.L.238.175; 1.L.238.240; 1.L.238.244; 1.L.239.228;

1.L.239.229; 1.L.239.230; 1.L.239.231; 1.L.239.236; 1.L.239.237; 1.L.239.238;
 1.L.239.239; 1.L.239.154; 1.L.239.157; 1.L.239.166; 1.L.239.169; 1.L.239.172;
 1.L.239.175; 1.L.239.240; 1.L.239.244; 1.L.154.228; 1.L.154.229; 1.L.154.230;
 1.L.154.231; 1.L.154.236; 1.L.154.237; 1.L.154.238; 1.L.154.239; 1.L.154.154;
 5 1.L.154.157; 1.L.154.166; 1.L.154.169; 1.L.154.172; 1.L.154.175; 1.L.154.240;
 1.L.154.244; 1.L.157.228; 1.L.157.229; 1.L.157.230; 1.L.157.231; 1.L.157.236;
 1.L.157.237; 1.L.157.238; 1.L.157.239; 1.L.157.154; 1.L.157.157; 1.L.157.166;
 1.L.157.169; 1.L.157.172; 1.L.157.175; 1.L.157.240; 1.L.157.244; 1.L.166.228;
 1.L.166.229; 1.L.166.230; 1.L.166.231; 1.L.166.236; 1.L.166.237; 1.L.166.238;
 10 1.L.166.239; 1.L.166.154; 1.L.166.157; 1.L.166.166; 1.L.166.169; 1.L.166.172;
 1.L.166.175; 1.L.166.240; 1.L.166.244; 1.L.169.228; 1.L.169.229; 1.L.169.230;
 1.L.169.231; 1.L.169.236; 1.L.169.237; 1.L.169.238; 1.L.169.239; 1.L.169.154;
 1.L.169.157; 1.L.169.166; 1.L.169.169; 1.L.169.172; 1.L.169.175; 1.L.169.240;
 1.L.169.244; 1.L.172.228; 1.L.172.229; 1.L.172.230; 1.L.172.231; 1.L.172.236;
 15 1.L.172.237; 1.L.172.238; 1.L.172.239; 1.L.172.154; 1.L.172.157; 1.L.172.166;
 1.L.172.169; 1.L.172.172; 1.L.172.175; 1.L.172.240; 1.L.172.244; 1.L.175.228;
 1.L.175.229; 1.L.175.230; 1.L.175.231; 1.L.175.236; 1.L.175.237; 1.L.175.238;
 1.L.175.239; 1.L.175.154; 1.L.175.157; 1.L.175.166; 1.L.175.169; 1.L.175.172;
 1.L.175.175; 1.L.175.240; 1.L.175.244; 1.L.240.228; 1.L.240.229; 1.L.240.230;
 20 1.L.240.231; 1.L.240.236; 1.L.240.237; 1.L.240.238; 1.L.240.239; 1.L.240.154;
 1.L.240.157; 1.L.240.166; 1.L.240.169; 1.L.240.172; 1.L.240.175; 1.L.240.240;
 1.L.240.244; 1.L.244.228; 1.L.244.229; 1.L.244.230; 1.L.244.231; 1.L.244.236;
 1.L.244.237; 1.L.244.238; 1.L.244.239; 1.L.244.154; 1.L.244.157; 1.L.244.166;
 1.L.244.169; 1.L.244.172; 1.L.244.175; 1.L.244.240; 1.L.244.244;

25

Prodrugs of 1.O

1.O.228.228; 1.O.228.229; 1.O.228.230; 1.O.228.231; 1.O.228.236;
 1.O.228.237; 1.O.228.238; 1.O.228.239; 1.O.228.154; 1.O.228.157;
 1.O.228.166; 1.O.228.169; 1.O.228.172; 1.O.228.175; 1.O.228.240;
 30 1.O.228.244; 1.O.229.228; 1.O.229.229; 1.O.229.230; 1.O.229.231;
 1.O.229.236; 1.O.229.237; 1.O.229.238; 1.O.229.239; 1.O.229.154;

- 1.O.229.157; 1.O.229.166; 1.O.229.169; 1.O.229.172; 1.O.229.175;
1.O.229.240; 1.O.229.244; 1.O.230.228; 1.O.230.229; 1.O.230.230;
1.O.230.231; 1.O.230.236; 1.O.230.237; 1.O.230.238; 1.O.230.239;
1.O.230.154; 1.O.230.157; 1.O.230.166; 1.O.230.169; 1.O.230.172;
5 1.O.230.175; 1.O.230.240; 1.O.230.244; 1.O.231.228; 1.O.231.229;
1.O.231.230; 1.O.231.231; 1.O.231.236; 1.O.231.237; 1.O.231.238;
1.O.231.239; 1.O.231.154; 1.O.231.157; 1.O.231.166; 1.O.231.169;
1.O.231.172; 1.O.231.175; 1.O.231.240; 1.O.231.244; 1.O.236.228;
1.O.236.229; 1.O.236.230; 1.O.236.231; 1.O.236.236; 1.O.236.237;
10 1.O.236.238; 1.O.236.239; 1.O.236.154; 1.O.236.157; 1.O.236.166;
1.O.236.169; 1.O.236.172; 1.O.236.175; 1.O.236.240; 1.O.236.244;
1.O.237.228; 1.O.237.229; 1.O.237.230; 1.O.237.231; 1.O.237.236;
1.O.237.237; 1.O.237.238; 1.O.237.239; 1.O.237.154; 1.O.237.157;
1.O.237.166; 1.O.237.169; 1.O.237.172; 1.O.237.175; 1.O.237.240;
15 1.O.237.244; 1.O.238.228; 1.O.238.229; 1.O.238.230; 1.O.238.231;
1.O.238.236; 1.O.238.237; 1.O.238.238; 1.O.238.239; 1.O.238.154;
1.O.238.157; 1.O.238.166; 1.O.238.169; 1.O.238.172; 1.O.238.175;
1.O.238.240; 1.O.238.244; 1.O.239.228; 1.O.239.229; 1.O.239.230;
1.O.239.231; 1.O.239.236; 1.O.239.237; 1.O.239.238; 1.O.239.239;
20 1.O.239.154; 1.O.239.157; 1.O.239.166; 1.O.239.169; 1.O.239.172;
1.O.239.175; 1.O.239.240; 1.O.239.244; 1.O.154.228; 1.O.154.229;
1.O.154.230; 1.O.154.231; 1.O.154.236; 1.O.154.237; 1.O.154.238;
1.O.154.239; 1.O.154.154; 1.O.154.157; 1.O.154.166; 1.O.154.169;
1.O.154.172; 1.O.154.175; 1.O.154.240; 1.O.154.244; 1.O.157.228;
25 1.O.157.229; 1.O.157.230; 1.O.157.231; 1.O.157.236; 1.O.157.237;
1.O.157.238; 1.O.157.239; 1.O.157.154; 1.O.157.157; 1.O.157.166;
1.O.157.169; 1.O.157.172; 1.O.157.175; 1.O.157.240; 1.O.157.244;
1.O.166.228; 1.O.166.229; 1.O.166.230; 1.O.166.231; 1.O.166.236;
1.O.166.237; 1.O.166.238; 1.O.166.239; 1.O.166.154; 1.O.166.157;
30 1.O.166.166; 1.O.166.169; 1.O.166.172; 1.O.166.175; 1.O.166.240;
1.O.166.244; 1.O.169.228; 1.O.169.229; 1.O.169.230; 1.O.169.231;

1.O.169.236; 1.O.169.237; 1.O.169.238; 1.O.169.239; 1.O.169.154;
 1.O.169.157; 1.O.169.166; 1.O.169.169; 1.O.169.172; 1.O.169.175;
 1.O.169.240; 1.O.169.244; 1.O.172.228; 1.O.172.229; 1.O.172.230;
 1.O.172.231; 1.O.172.236; 1.O.172.237; 1.O.172.238; 1.O.172.239;
 5 1.O.172.154; 1.O.172.157; 1.O.172.166; 1.O.172.169; 1.O.172.172;
 1.O.172.175; 1.O.172.240; 1.O.172.244; 1.O.175.228; 1.O.175.229;
 1.O.175.230; 1.O.175.231; 1.O.175.236; 1.O.175.237; 1.O.175.238;
 1.O.175.239; 1.O.175.154; 1.O.175.157; 1.O.175.166; 1.O.175.169;
 1.O.175.172; 1.O.175.175; 1.O.175.240; 1.O.175.244; 1.O.240.228;
 10 1.O.240.229; 1.O.240.230; 1.O.240.231; 1.O.240.236; 1.O.240.237;
 1.O.240.238; 1.O.240.239; 1.O.240.154; 1.O.240.157; 1.O.240.166;
 1.O.240.169; 1.O.240.172; 1.O.240.175; 1.O.240.240; 1.O.240.244;
 1.O.244.228; 1.O.244.229; 1.O.244.230; 1.O.244.231; 1.O.244.236;
 1.O.244.237; 1.O.244.238; 1.O.244.239; 1.O.244.154; 1.O.244.157;
 15 1.O.244.166; 1.O.244.169; 1.O.244.172; 1.O.244.175; 1.O.244.240;
 1.O.244.244;

Prodrugs of 1.P

1.P.228.228; 1.P.228.229; 1.P.228.230; 1.P.228.231; 1.P.228.236;
 20 1.P.228.237; 1.P.228.238; 1.P.228.239; 1.P.228.154; 1.P.228.157; 1.P.228.166;
 1.P.228.169; 1.P.228.172; 1.P.228.175; 1.P.228.240; 1.P.228.244; 1.P.229.228;
 1.P.229.229; 1.P.229.230; 1.P.229.231; 1.P.229.236; 1.P.229.237; 1.P.229.238;
 1.P.229.239; 1.P.229.154; 1.P.229.157; 1.P.229.166; 1.P.229.169; 1.P.229.172;
 1.P.229.175; 1.P.229.240; 1.P.229.244; 1.P.230.228; 1.P.230.229; 1.P.230.230;
 25 1.P.230.231; 1.P.230.236; 1.P.230.237; 1.P.230.238; 1.P.230.239; 1.P.230.154;
 1.P.230.157; 1.P.230.166; 1.P.230.169; 1.P.230.172; 1.P.230.175; 1.P.230.240;
 1.P.230.244; 1.P.231.228; 1.P.231.229; 1.P.231.230; 1.P.231.231; 1.P.231.236;
 1.P.231.237; 1.P.231.238; 1.P.231.239; 1.P.231.154; 1.P.231.157; 1.P.231.166;
 1.P.231.169; 1.P.231.172; 1.P.231.175; 1.P.231.240; 1.P.231.244; 1.P.236.228;
 30 1.P.236.229; 1.P.236.230; 1.P.236.231; 1.P.236.236; 1.P.236.237; 1.P.236.238;
 1.P.236.239; 1.P.236.154; 1.P.236.157; 1.P.236.166; 1.P.236.169; 1.P.236.172;

1.P.236.175; 1.P.236.240; 1.P.236.244; 1.P.237.228; 1.P.237.229; 1.P.237.230;
 1.P.237.231; 1.P.237.236; 1.P.237.237; 1.P.237.238; 1.P.237.239; 1.P.237.154;
 1.P.237.157; 1.P.237.166; 1.P.237.169; 1.P.237.172; 1.P.237.175; 1.P.237.240;
 1.P.237.244; 1.P.238.228; 1.P.238.229; 1.P.238.230; 1.P.238.231; 1.P.238.236;
 5 1.P.238.237; 1.P.238.238; 1.P.238.239; 1.P.238.154; 1.P.238.157; 1.P.238.166;
 1.P.238.169; 1.P.238.172; 1.P.238.175; 1.P.238.240; 1.P.238.244; 1.P.239.228;
 1.P.239.229; 1.P.239.230; 1.P.239.231; 1.P.239.236; 1.P.239.237; 1.P.239.238;
 1.P.239.239; 1.P.239.154; 1.P.239.157; 1.P.239.166; 1.P.239.169; 1.P.239.172;
 1.P.239.175; 1.P.239.240; 1.P.239.244; 1.P.154.228; 1.P.154.229; 1.P.154.230;
 10 1.P.154.231; 1.P.154.236; 1.P.154.237; 1.P.154.238; 1.P.154.239; 1.P.154.154;
 1.P.154.157; 1.P.154.166; 1.P.154.169; 1.P.154.172; 1.P.154.175; 1.P.154.240;
 1.P.154.244; 1.P.157.228; 1.P.157.229; 1.P.157.230; 1.P.157.231; 1.P.157.236;
 1.P.157.237; 1.P.157.238; 1.P.157.239; 1.P.157.154; 1.P.157.157; 1.P.157.166;
 1.P.157.169; 1.P.157.172; 1.P.157.175; 1.P.157.240; 1.P.157.244; 1.P.166.228;
 15 1.P.166.229; 1.P.166.230; 1.P.166.231; 1.P.166.236; 1.P.166.237; 1.P.166.238;
 1.P.166.239; 1.P.166.154; 1.P.166.157; 1.P.166.166; 1.P.166.169; 1.P.166.172;
 1.P.166.175; 1.P.166.240; 1.P.166.244; 1.P.169.228; 1.P.169.229; 1.P.169.230;
 1.P.169.231; 1.P.169.236; 1.P.169.237; 1.P.169.238; 1.P.169.239; 1.P.169.154;
 1.P.169.157; 1.P.169.166; 1.P.169.169; 1.P.169.172; 1.P.169.175; 1.P.169.240;
 20 1.P.169.244; 1.P.172.228; 1.P.172.229; 1.P.172.230; 1.P.172.231; 1.P.172.236;
 1.P.172.237; 1.P.172.238; 1.P.172.239; 1.P.172.154; 1.P.172.157; 1.P.172.166;
 1.P.172.169; 1.P.172.172; 1.P.172.175; 1.P.172.240; 1.P.172.244; 1.P.175.228;
 1.P.175.229; 1.P.175.230; 1.P.175.231; 1.P.175.236; 1.P.175.237; 1.P.175.238;
 1.P.175.239; 1.P.175.154; 1.P.175.157; 1.P.175.166; 1.P.175.169; 1.P.175.172;
 25 1.P.175.175; 1.P.175.240; 1.P.175.244; 1.P.240.228; 1.P.240.229; 1.P.240.230;
 1.P.240.231; 1.P.240.236; 1.P.240.237; 1.P.240.238; 1.P.240.239; 1.P.240.154;
 1.P.240.157; 1.P.240.166; 1.P.240.169; 1.P.240.172; 1.P.240.175; 1.P.240.240;
 1.P.240.244; 1.P.244.228; 1.P.244.229; 1.P.244.230; 1.P.244.231; 1.P.244.236;
 1.P.244.237; 1.P.244.238; 1.P.244.239; 1.P.244.154; 1.P.244.157; 1.P.244.166;
 30 1.P.244.169; 1.P.244.172; 1.P.244.175; 1.P.244.240; 1.P.244.244;

Prodrugs of 1.U

- 1.U.228.228; 1.U.228.229; 1.U.228.230; 1.U.228.231; 1.U.228.236;
1.U.228.237; 1.U.228.238; 1.U.228.239; 1.U.228.154; 1.U.228.157;
1.U.228.166; 1.U.228.169; 1.U.228.172; 1.U.228.175; 1.U.228.240;
5 1.U.228.244; 1.U.229.228; 1.U.229.229; 1.U.229.230; 1.U.229.231;
1.U.229.236; 1.U.229.237; 1.U.229.238; 1.U.229.239; 1.U.229.154;
1.U.229.157; 1.U.229.166; 1.U.229.169; 1.U.229.172; 1.U.229.175;
1.U.229.240; 1.U.229.244; 1.U.230.228; 1.U.230.229; 1.U.230.230;
1.U.230.231; 1.U.230.236; 1.U.230.237; 1.U.230.238; 1.U.230.239;
10 1.U.230.154; 1.U.230.157; 1.U.230.166; 1.U.230.169; 1.U.230.172;
1.U.230.175; 1.U.230.240; 1.U.230.244; 1.U.231.228; 1.U.231.229;
1.U.231.230; 1.U.231.231; 1.U.231.236; 1.U.231.237; 1.U.231.238;
1.U.231.239; 1.U.231.154; 1.U.231.157; 1.U.231.166; 1.U.231.169;
1.U.231.172; 1.U.231.175; 1.U.231.240; 1.U.231.244; 1.U.236.228;
15 1.U.236.229; 1.U.236.230; 1.U.236.231; 1.U.236.236; 1.U.236.237;
1.U.236.238; 1.U.236.239; 1.U.236.154; 1.U.236.157; 1.U.236.166;
1.U.236.169; 1.U.236.172; 1.U.236.175; 1.U.236.240; 1.U.236.244;
1.U.237.228; 1.U.237.229; 1.U.237.230; 1.U.237.231; 1.U.237.236;
1.U.237.237; 1.U.237.238; 1.U.237.239; 1.U.237.154; 1.U.237.157;
20 1.U.237.166; 1.U.237.169; 1.U.237.172; 1.U.237.175; 1.U.237.240;
1.U.237.244; 1.U.238.228; 1.U.238.229; 1.U.238.230; 1.U.238.231;
1.U.238.236; 1.U.238.237; 1.U.238.238; 1.U.238.239; 1.U.238.154;
1.U.238.157; 1.U.238.166; 1.U.238.169; 1.U.238.172; 1.U.238.175;
1.U.238.240; 1.U.238.244; 1.U.239.228; 1.U.239.229; 1.U.239.230;
25 1.U.239.231; 1.U.239.236; 1.U.239.237; 1.U.239.238; 1.U.239.239;
1.U.239.154; 1.U.239.157; 1.U.239.166; 1.U.239.169; 1.U.239.172;
1.U.239.175; 1.U.239.240; 1.U.239.244; 1.U.154.228; 1.U.154.229;
1.U.154.230; 1.U.154.231; 1.U.154.236; 1.U.154.237; 1.U.154.238;
1.U.154.239; 1.U.154.154; 1.U.154.157; 1.U.154.166; 1.U.154.169;
30 1.U.154.172; 1.U.154.175; 1.U.154.240; 1.U.154.244; 1.U.157.228;
1.U.157.229; 1.U.157.230; 1.U.157.231; 1.U.157.236; 1.U.157.237;

- 1.U.157.238; 1.U.157.239; 1.U.157.154; 1.U.157.157; 1.U.157.166;
 1.U.157.169; 1.U.157.172; 1.U.157.175; 1.U.157.240; 1.U.157.244;
 1.U.166.228; 1.U.166.229; 1.U.166.230; 1.U.166.231; 1.U.166.236;
 1.U.166.237; 1.U.166.238; 1.U.166.239; 1.U.166.154; 1.U.166.157;
 5 1.U.166.166; 1.U.166.169; 1.U.166.172; 1.U.166.175; 1.U.166.240;
 1.U.166.244; 1.U.169.228; 1.U.169.229; 1.U.169.230; 1.U.169.231;
 1.U.169.236; 1.U.169.237; 1.U.169.238; 1.U.169.239; 1.U.169.154;
 1.U.169.157; 1.U.169.166; 1.U.169.169; 1.U.169.172; 1.U.169.175;
 1.U.169.240; 1.U.169.244; 1.U.172.228; 1.U.172.229; 1.U.172.230;
 10 1.U.172.231; 1.U.172.236; 1.U.172.237; 1.U.172.238; 1.U.172.239;
 1.U.172.154; 1.U.172.157; 1.U.172.166; 1.U.172.169; 1.U.172.172;
 1.U.172.175; 1.U.172.240; 1.U.172.244; 1.U.175.228; 1.U.175.229;
 1.U.175.230; 1.U.175.231; 1.U.175.236; 1.U.175.237; 1.U.175.238;
 1.U.175.239; 1.U.175.154; 1.U.175.157; 1.U.175.166; 1.U.175.169;
 15 1.U.175.172; 1.U.175.175; 1.U.175.240; 1.U.175.244; 1.U.240.228;
 1.U.240.229; 1.U.240.230; 1.U.240.231; 1.U.240.236; 1.U.240.237;
 1.U.240.238; 1.U.240.239; 1.U.240.154; 1.U.240.157; 1.U.240.166;
 1.U.240.169; 1.U.240.172; 1.U.240.175; 1.U.240.240; 1.U.240.244;
 1.U.244.228; 1.U.244.229; 1.U.244.230; 1.U.244.231; 1.U.244.236;
 20 1.U.244.237; 1.U.244.238; 1.U.244.239; 1.U.244.154; 1.U.244.157;
 1.U.244.166; 1.U.244.169; 1.U.244.172; 1.U.244.175; 1.U.244.240;
 1.U.244.244;

Prodrugs of 1.W

- 25 1.W.228.228; 1.W.228.229; 1.W.228.230; 1.W.228.231; 1.W.228.236;
 1.W.228.237; 1.W.228.238; 1.W.228.239; 1.W.228.154; 1.W.228.157;
 1.W.228.166; 1.W.228.169; 1.W.228.172; 1.W.228.175; 1.W.228.240;
 1.W.228.244; 1.W.229.228; 1.W.229.229; 1.W.229.230; 1.W.229.231;
 1.W.229.236; 1.W.229.237; 1.W.229.238; 1.W.229.239; 1.W.229.154;
 30 1.W.229.157; 1.W.229.166; 1.W.229.169; 1.W.229.172; 1.W.229.175;
 1.W.229.240; 1.W.229.244; 1.W.230.228; 1.W.230.229; 1.W.230.230;

1.W.230.231; 1.W.230.236; 1.W.230.237; 1.W.230.238; 1.W.230.239;
1.W.230.154; 1.W.230.157; 1.W.230.166; 1.W.230.169; 1.W.230.172;
1.W.230.175; 1.W.230.240; 1.W.230.244; 1.W.231.228; 1.W.231.229;
1.W.231.230; 1.W.231.231; 1.W.231.236; 1.W.231.237; 1.W.231.238;
5 1.W.231.239; 1.W.231.154; 1.W.231.157; 1.W.231.166; 1.W.231.169;
1.W.231.172; 1.W.231.175; 1.W.231.240; 1.W.231.244; 1.W.236.228;
1.W.236.229; 1.W.236.230; 1.W.236.231; 1.W.236.236; 1.W.236.237;
1.W.236.238; 1.W.236.239; 1.W.236.154; 1.W.236.157; 1.W.236.166;
1.W.236.169; 1.W.236.172; 1.W.236.175; 1.W.236.240; 1.W.236.244;
10 1.W.237.228; 1.W.237.229; 1.W.237.230; 1.W.237.231; 1.W.237.236;
1.W.237.237; 1.W.237.238; 1.W.237.239; 1.W.237.154; 1.W.237.157;
1.W.237.166; 1.W.237.169; 1.W.237.172; 1.W.237.175; 1.W.237.240;
1.W.237.244; 1.W.238.228; 1.W.238.229; 1.W.238.230; 1.W.238.231;
1.W.238.236; 1.W.238.237; 1.W.238.238; 1.W.238.239; 1.W.238.154;
15 1.W.238.157; 1.W.238.166; 1.W.238.169; 1.W.238.172; 1.W.238.175;
1.W.238.240; 1.W.238.244; 1.W.239.228; 1.W.239.229; 1.W.239.230;
1.W.239.231; 1.W.239.236; 1.W.239.237; 1.W.239.238; 1.W.239.239;
1.W.239.154; 1.W.239.157; 1.W.239.166; 1.W.239.169; 1.W.239.172;
1.W.239.175; 1.W.239.240; 1.W.239.244; 1.W.154.228; 1.W.154.229;
20 1.W.154.230; 1.W.154.231; 1.W.154.236; 1.W.154.237; 1.W.154.238;
1.W.154.239; 1.W.154.154; 1.W.154.157; 1.W.154.166; 1.W.154.169;
1.W.154.172; 1.W.154.175; 1.W.154.240; 1.W.154.244; 1.W.157.228;
1.W.157.229; 1.W.157.230; 1.W.157.231; 1.W.157.236; 1.W.157.237;
1.W.157.238; 1.W.157.239; 1.W.157.154; 1.W.157.157; 1.W.157.166;
25 1.W.157.169; 1.W.157.172; 1.W.157.175; 1.W.157.240; 1.W.157.244;
1.W.166.228; 1.W.166.229; 1.W.166.230; 1.W.166.231; 1.W.166.236;
1.W.166.237; 1.W.166.238; 1.W.166.239; 1.W.166.154; 1.W.166.157;
1.W.166.166; 1.W.166.169; 1.W.166.172; 1.W.166.175; 1.W.166.240;
1.W.166.244; 1.W.169.228; 1.W.169.229; 1.W.169.230; 1.W.169.231;
30 1.W.169.236; 1.W.169.237; 1.W.169.238; 1.W.169.239; 1.W.169.154;
1.W.169.157; 1.W.169.166; 1.W.169.169; 1.W.169.172; 1.W.169.175;

1.W.169.240; 1.W.169.244; 1.W.172.228; 1.W.172.229; 1.W.172.230;
1.W.172.231; 1.W.172.236; 1.W.172.237; 1.W.172.238; 1.W.172.239;
1.W.172.154; 1.W.172.157; 1.W.172.166; 1.W.172.169; 1.W.172.172;
1.W.172.175; 1.W.172.240; 1.W.172.244; 1.W.175.228; 1.W.175.229;
5 1.W.175.230; 1.W.175.231; 1.W.175.236; 1.W.175.237; 1.W.175.238;
1.W.175.239; 1.W.175.154; 1.W.175.157; 1.W.175.166; 1.W.175.169;
1.W.175.172; 1.W.175.175; 1.W.175.240; 1.W.175.244; 1.W.240.228;
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1.W.240.238; 1.W.240.239; 1.W.240.154; 1.W.240.157; 1.W.240.166;
10 1.W.240.169; 1.W.240.172; 1.W.240.175; 1.W.240.240; 1.W.240.244;
1.W.244.228; 1.W.244.229; 1.W.244.230; 1.W.244.231; 1.W.244.236;
1.W.244.237; 1.W.244.238; 1.W.244.239; 1.W.244.154; 1.W.244.157;
1.W.244.166; 1.W.244.169; 1.W.244.172; 1.W.244.175; 1.W.244.240;
1.W.244.244;

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Prodrugs of 1.Y

1.Y.228.228; 1.Y.228.229; 1.Y.228.230; 1.Y.228.231; 1.Y.228.236;
1.Y.228.237; 1.Y.228.238; 1.Y.228.239; 1.Y.228.154; 1.Y.228.157; 1.Y.228.166;
1.Y.228.169; 1.Y.228.172; 1.Y.228.175; 1.Y.228.240; 1.Y.228.244; 1.Y.229.228;
20 1.Y.229.229; 1.Y.229.230; 1.Y.229.231; 1.Y.229.236; 1.Y.229.237; 1.Y.229.238;
1.Y.229.239; 1.Y.229.154; 1.Y.229.157; 1.Y.229.166; 1.Y.229.169; 1.Y.229.172;
1.Y.229.175; 1.Y.229.240; 1.Y.229.244; 1.Y.230.228; 1.Y.230.229; 1.Y.230.230;
1.Y.230.231; 1.Y.230.236; 1.Y.230.237; 1.Y.230.238; 1.Y.230.239; 1.Y.230.154;
1.Y.230.157; 1.Y.230.166; 1.Y.230.169; 1.Y.230.172; 1.Y.230.175; 1.Y.230.240;
25 1.Y.230.244; 1.Y.231.228; 1.Y.231.229; 1.Y.231.230; 1.Y.231.231; 1.Y.231.236;
1.Y.231.237; 1.Y.231.238; 1.Y.231.239; 1.Y.231.154; 1.Y.231.157; 1.Y.231.166;
1.Y.231.169; 1.Y.231.172; 1.Y.231.175; 1.Y.231.240; 1.Y.231.244; 1.Y.236.228;
1.Y.236.229; 1.Y.236.230; 1.Y.236.231; 1.Y.236.236; 1.Y.236.237; 1.Y.236.238;
1.Y.236.239; 1.Y.236.154; 1.Y.236.157; 1.Y.236.166; 1.Y.236.169; 1.Y.236.172;
30 1.Y.236.175; 1.Y.236.240; 1.Y.236.244; 1.Y.237.228; 1.Y.237.229; 1.Y.237.230;
1.Y.237.231; 1.Y.237.236; 1.Y.237.237; 1.Y.237.238; 1.Y.237.239; 1.Y.237.154;

1.Y.237.157; 1.Y.237.166; 1.Y.237.169; 1.Y.237.172; 1.Y.237.175; 1.Y.237.240;
1.Y.237.244; 1.Y.238.228; 1.Y.238.229; 1.Y.238.230; 1.Y.238.231; 1.Y.238.236;
1.Y.238.237; 1.Y.238.238; 1.Y.238.239; 1.Y.238.154; 1.Y.238.157; 1.Y.238.166;
1.Y.238.169; 1.Y.238.172; 1.Y.238.175; 1.Y.238.240; 1.Y.238.244; 1.Y.239.228;
5 1.Y.239.229; 1.Y.239.230; 1.Y.239.231; 1.Y.239.236; 1.Y.239.237; 1.Y.239.238;
1.Y.239.239; 1.Y.239.154; 1.Y.239.157; 1.Y.239.166; 1.Y.239.169; 1.Y.239.172;
1.Y.239.175; 1.Y.239.240; 1.Y.239.244; 1.Y.154.228; 1.Y.154.229; 1.Y.154.230;
1.Y.154.231; 1.Y.154.236; 1.Y.154.237; 1.Y.154.238; 1.Y.154.239; 1.Y.154.154;
1.Y.154.157; 1.Y.154.166; 1.Y.154.169; 1.Y.154.172; 1.Y.154.175; 1.Y.154.240;
10 1.Y.154.244; 1.Y.157.228; 1.Y.157.229; 1.Y.157.230; 1.Y.157.231; 1.Y.157.236;
1.Y.157.237; 1.Y.157.238; 1.Y.157.239; 1.Y.157.154; 1.Y.157.157; 1.Y.157.166;
1.Y.157.169; 1.Y.157.172; 1.Y.157.175; 1.Y.157.240; 1.Y.157.244; 1.Y.166.228;
1.Y.166.229; 1.Y.166.230; 1.Y.166.231; 1.Y.166.236; 1.Y.166.237; 1.Y.166.238;
1.Y.166.239; 1.Y.166.154; 1.Y.166.157; 1.Y.166.166; 1.Y.166.169; 1.Y.166.172;
15 1.Y.166.175; 1.Y.166.240; 1.Y.166.244; 1.Y.169.228; 1.Y.169.229; 1.Y.169.230;
1.Y.169.231; 1.Y.169.236; 1.Y.169.237; 1.Y.169.238; 1.Y.169.239; 1.Y.169.154;
1.Y.169.157; 1.Y.169.166; 1.Y.169.169; 1.Y.169.172; 1.Y.169.175; 1.Y.169.240;
1.Y.169.244; 1.Y.172.228; 1.Y.172.229; 1.Y.172.230; 1.Y.172.231; 1.Y.172.236;
1.Y.172.237; 1.Y.172.238; 1.Y.172.239; 1.Y.172.154; 1.Y.172.157; 1.Y.172.166;
20 1.Y.172.169; 1.Y.172.172; 1.Y.172.175; 1.Y.172.240; 1.Y.172.244; 1.Y.175.228;
1.Y.175.229; 1.Y.175.230; 1.Y.175.231; 1.Y.175.236; 1.Y.175.237; 1.Y.175.238;
1.Y.175.239; 1.Y.175.154; 1.Y.175.157; 1.Y.175.166; 1.Y.175.169; 1.Y.175.172;
1.Y.175.175; 1.Y.175.240; 1.Y.175.244; 1.Y.240.228; 1.Y.240.229; 1.Y.240.230;
1.Y.240.231; 1.Y.240.236; 1.Y.240.237; 1.Y.240.238; 1.Y.240.239; 1.Y.240.154;
25 1.Y.240.157; 1.Y.240.166; 1.Y.240.169; 1.Y.240.172; 1.Y.240.175; 1.Y.240.240;
1.Y.240.244; 1.Y.244.228; 1.Y.244.229; 1.Y.244.230; 1.Y.244.231; 1.Y.244.236;
1.Y.244.237; 1.Y.244.238; 1.Y.244.239; 1.Y.244.154; 1.Y.244.157; 1.Y.244.166;
1.Y.244.169; 1.Y.244.172; 1.Y.244.175; 1.Y.244.240; 1.Y.244.244;

30 Prodrugs of 2.B

- 2.B.228.228; 2.B.228.229; 2.B.228.230; 2.B.228.231; 2.B.228.236;
 2.B.228.237; 2.B.228.238; 2.B.228.239; 2.B.228.154; 2.B.228.157; 2.B.228.166;
 2.B.228.169; 2.B.228.172; 2.B.228.175; 2.B.228.240; 2.B.228.244; 2.B.229.228;
 2.B.229.229; 2.B.229.230; 2.B.229.231; 2.B.229.236; 2.B.229.237; 2.B.229.238;
 5 2.B.229.239; 2.B.229.154; 2.B.229.157; 2.B.229.166; 2.B.229.169; 2.B.229.172;
 2.B.229.175; 2.B.229.240; 2.B.229.244; 2.B.230.228; 2.B.230.229; 2.B.230.230;
 2.B.230.231; 2.B.230.236; 2.B.230.237; 2.B.230.238; 2.B.230.239; 2.B.230.154;
 2.B.230.157; 2.B.230.166; 2.B.230.169; 2.B.230.172; 2.B.230.175; 2.B.230.240;
 2.B.230.244; 2.B.231.228; 2.B.231.229; 2.B.231.230; 2.B.231.231; 2.B.231.236;
 10 2.B.231.237; 2.B.231.238; 2.B.231.239; 2.B.231.154; 2.B.231.157; 2.B.231.166;
 2.B.231.169; 2.B.231.172; 2.B.231.175; 2.B.231.240; 2.B.231.244; 2.B.236.228;
 2.B.236.229; 2.B.236.230; 2.B.236.231; 2.B.236.236; 2.B.236.237; 2.B.236.238;
 2.B.236.239; 2.B.236.154; 2.B.236.157; 2.B.236.166; 2.B.236.169; 2.B.236.172;
 2.B.236.175; 2.B.236.240; 2.B.236.244; 2.B.237.228; 2.B.237.229; 2.B.237.230;
 15 2.B.237.231; 2.B.237.236; 2.B.237.237; 2.B.237.238; 2.B.237.239; 2.B.237.154;
 2.B.237.157; 2.B.237.166; 2.B.237.169; 2.B.237.172; 2.B.237.175; 2.B.237.240;
 2.B.237.244; 2.B.238.228; 2.B.238.229; 2.B.238.230; 2.B.238.231; 2.B.238.236;
 2.B.238.237; 2.B.238.238; 2.B.238.239; 2.B.238.154; 2.B.238.157; 2.B.238.166;
 2.B.238.169; 2.B.238.172; 2.B.238.175; 2.B.238.240; 2.B.238.244; 2.B.239.228;
 20 2.B.239.229; 2.B.239.230; 2.B.239.231; 2.B.239.236; 2.B.239.237; 2.B.239.238;
 2.B.239.239; 2.B.239.154; 2.B.239.157; 2.B.239.166; 2.B.239.169; 2.B.239.172;
 2.B.239.175; 2.B.239.240; 2.B.239.244; 2.B.154.228; 2.B.154.229; 2.B.154.230;
 2.B.154.231; 2.B.154.236; 2.B.154.237; 2.B.154.238; 2.B.154.239; 2.B.154.154;
 2.B.154.157; 2.B.154.166; 2.B.154.169; 2.B.154.172; 2.B.154.175; 2.B.154.240;
 25 2.B.154.244; 2.B.157.228; 2.B.157.229; 2.B.157.230; 2.B.157.231; 2.B.157.236;
 2.B.157.237; 2.B.157.238; 2.B.157.239; 2.B.157.154; 2.B.157.157; 2.B.157.166;
 2.B.157.169; 2.B.157.172; 2.B.157.175; 2.B.157.240; 2.B.157.244; 2.B.166.228;
 2.B.166.229; 2.B.166.230; 2.B.166.231; 2.B.166.236; 2.B.166.237; 2.B.166.238;
 2.B.166.239; 2.B.166.154; 2.B.166.157; 2.B.166.166; 2.B.166.169; 2.B.166.172;
 30 2.B.166.175; 2.B.166.240; 2.B.166.244; 2.B.169.228; 2.B.169.229; 2.B.169.230;
 2.B.169.231; 2.B.169.236; 2.B.169.237; 2.B.169.238; 2.B.169.239; 2.B.169.154;

2.B.169.157; 2.B.169.166; 2.B.169.169; 2.B.169.172; 2.B.169.175; 2.B.169.240;
 2.B.169.244; 2.B.172.228; 2.B.172.229; 2.B.172.230; 2.B.172.231; 2.B.172.236;
 2.B.172.237; 2.B.172.238; 2.B.172.239; 2.B.172.154; 2.B.172.157; 2.B.172.166;
 2.B.172.169; 2.B.172.172; 2.B.172.175; 2.B.172.240; 2.B.172.244; 2.B.175.228;
 5 2.B.175.229; 2.B.175.230; 2.B.175.231; 2.B.175.236; 2.B.175.237; 2.B.175.238;
 2.B.175.239; 2.B.175.154; 2.B.175.157; 2.B.175.166; 2.B.175.169; 2.B.175.172;
 2.B.175.175; 2.B.175.240; 2.B.175.244; 2.B.240.228; 2.B.240.229; 2.B.240.230;
 2.B.240.231; 2.B.240.236; 2.B.240.237; 2.B.240.238; 2.B.240.239; 2.B.240.154;
 2.B.240.157; 2.B.240.166; 2.B.240.169; 2.B.240.172; 2.B.240.175; 2.B.240.240;
 10 2.B.240.244; 2.B.244.228; 2.B.244.229; 2.B.244.230; 2.B.244.231; 2.B.244.236;
 2.B.244.237; 2.B.244.238; 2.B.244.239; 2.B.244.154; 2.B.244.157; 2.B.244.166;
 2.B.244.169; 2.B.244.172; 2.B.244.175; 2.B.244.240; 2.B.244.244;

Prodrugs of 2.D

15 2.D.228.228; 2.D.228.229; 2.D.228.230; 2.D.228.231; 2.D.228.236;
 2.D.228.237; 2.D.228.238; 2.D.228.239; 2.D.228.154; 2.D.228.157;
 2.D.228.166; 2.D.228.169; 2.D.228.172; 2.D.228.175; 2.D.228.240;
 2.D.228.244; 2.D.229.228; 2.D.229.229; 2.D.229.230; 2.D.229.231;
 2.D.229.236; 2.D.229.237; 2.D.229.238; 2.D.229.239; 2.D.229.154;
 20 2.D.229.157; 2.D.229.166; 2.D.229.169; 2.D.229.172; 2.D.229.175;
 2.D.229.240; 2.D.229.244; 2.D.230.228; 2.D.230.229; 2.D.230.230;
 2.D.230.231; 2.D.230.236; 2.D.230.237; 2.D.230.238; 2.D.230.239;
 2.D.230.154; 2.D.230.157; 2.D.230.166; 2.D.230.169; 2.D.230.172;
 2.D.230.175; 2.D.230.240; 2.D.230.244; 2.D.231.228; 2.D.231.229;
 25 2.D.231.230; 2.D.231.231; 2.D.231.236; 2.D.231.237; 2.D.231.238;
 2.D.231.239; 2.D.231.154; 2.D.231.157; 2.D.231.166; 2.D.231.169;
 2.D.231.172; 2.D.231.175; 2.D.231.240; 2.D.231.244; 2.D.236.228;
 2.D.236.229; 2.D.236.230; 2.D.236.231; 2.D.236.236; 2.D.236.237;
 2.D.236.238; 2.D.236.239; 2.D.236.154; 2.D.236.157; 2.D.236.166;
 30 2.D.236.169; 2.D.236.172; 2.D.236.175; 2.D.236.240; 2.D.236.244;
 2.D.237.228; 2.D.237.229; 2.D.237.230; 2.D.237.231; 2.D.237.236;

- 2.D.237.237; 2.D.237.238; 2.D.237.239; 2.D.237.154; 2.D.237.157;
2.D.237.166; 2.D.237.169; 2.D.237.172; 2.D.237.175; 2.D.237.240;
2.D.237.244; 2.D.238.228; 2.D.238.229; 2.D.238.230; 2.D.238.231;
2.D.238.236; 2.D.238.237; 2.D.238.238; 2.D.238.239; 2.D.238.154;
5 2.D.238.157; 2.D.238.166; 2.D.238.169; 2.D.238.172; 2.D.238.175;
2.D.238.240; 2.D.238.244; 2.D.239.228; 2.D.239.229; 2.D.239.230;
2.D.239.231; 2.D.239.236; 2.D.239.237; 2.D.239.238; 2.D.239.239;
2.D.239.154; 2.D.239.157; 2.D.239.166; 2.D.239.169; 2.D.239.172;
2.D.239.175; 2.D.239.240; 2.D.239.244; 2.D.154.228; 2.D.154.229;
10 2.D.154.230; 2.D.154.231; 2.D.154.236; 2.D.154.237; 2.D.154.238;
2.D.154.239; 2.D.154.154; 2.D.154.157; 2.D.154.166; 2.D.154.169;
2.D.154.172; 2.D.154.175; 2.D.154.240; 2.D.154.244; 2.D.157.228;
2.D.157.229; 2.D.157.230; 2.D.157.231; 2.D.157.236; 2.D.157.237;
2.D.157.238; 2.D.157.239; 2.D.157.154; 2.D.157.157; 2.D.157.166;
15 2.D.157.169; 2.D.157.172; 2.D.157.175; 2.D.157.240; 2.D.157.244;
2.D.166.228; 2.D.166.229; 2.D.166.230; 2.D.166.231; 2.D.166.236;
2.D.166.237; 2.D.166.238; 2.D.166.239; 2.D.166.154; 2.D.166.157;
2.D.166.166; 2.D.166.169; 2.D.166.172; 2.D.166.175; 2.D.166.240;
2.D.166.244; 2.D.169.228; 2.D.169.229; 2.D.169.230; 2.D.169.231;
20 2.D.169.236; 2.D.169.237; 2.D.169.238; 2.D.169.239; 2.D.169.154;
2.D.169.157; 2.D.169.166; 2.D.169.169; 2.D.169.172; 2.D.169.175;
2.D.169.240; 2.D.169.244; 2.D.172.228; 2.D.172.229; 2.D.172.230;
2.D.172.231; 2.D.172.236; 2.D.172.237; 2.D.172.238; 2.D.172.239;
2.D.172.154; 2.D.172.157; 2.D.172.166; 2.D.172.169; 2.D.172.172;
25 2.D.172.175; 2.D.172.240; 2.D.172.244; 2.D.175.228; 2.D.175.229;
2.D.175.230; 2.D.175.231; 2.D.175.236; 2.D.175.237; 2.D.175.238;
2.D.175.239; 2.D.175.154; 2.D.175.157; 2.D.175.166; 2.D.175.169;
2.D.175.172; 2.D.175.175; 2.D.175.240; 2.D.175.244; 2.D.240.228;
2.D.240.229; 2.D.240.230; 2.D.240.231; 2.D.240.236; 2.D.240.237;
30 2.D.240.238; 2.D.240.239; 2.D.240.154; 2.D.240.157; 2.D.240.166;
2.D.240.169; 2.D.240.172; 2.D.240.175; 2.D.240.240; 2.D.240.244;

2.D.244.228; 2.D.244.229; 2.D.244.230; 2.D.244.231; 2.D.244.236;
 2.D.244.237; 2.D.244.238; 2.D.244.239; 2.D.244.154; 2.D.244.157;
 2.D.244.166; 2.D.244.169; 2.D.244.172; 2.D.244.175; 2.D.244.240;
 2.D.244.244;

5

Prodrugs of 2.E

2.E.228.228; 2.E.228.229; 2.E.228.230; 2.E.228.231; 2.E.228.236;
 2.E.228.237; 2.E.228.238; 2.E.228.239; 2.E.228.154; 2.E.228.157; 2.E.228.166;
 2.E.228.169; 2.E.228.172; 2.E.228.175; 2.E.228.240; 2.E.228.244; 2.E.229.228;
 10 2.E.229.229; 2.E.229.230; 2.E.229.231; 2.E.229.236; 2.E.229.237; 2.E.229.238;
 2.E.229.239; 2.E.229.154; 2.E.229.157; 2.E.229.166; 2.E.229.169; 2.E.229.172;
 2.E.229.175; 2.E.229.240; 2.E.229.244; 2.E.230.228; 2.E.230.229; 2.E.230.230;
 2.E.230.231; 2.E.230.236; 2.E.230.237; 2.E.230.238; 2.E.230.239; 2.E.230.154;
 2.E.230.157; 2.E.230.166; 2.E.230.169; 2.E.230.172; 2.E.230.175; 2.E.230.240;
 15 2.E.230.244; 2.E.231.228; 2.E.231.229; 2.E.231.230; 2.E.231.231; 2.E.231.236;
 2.E.231.237; 2.E.231.238; 2.E.231.239; 2.E.231.154; 2.E.231.157; 2.E.231.166;
 2.E.231.169; 2.E.231.172; 2.E.231.175; 2.E.231.240; 2.E.231.244; 2.E.236.228;
 2.E.236.229; 2.E.236.230; 2.E.236.231; 2.E.236.236; 2.E.236.237; 2.E.236.238;
 2.E.236.239; 2.E.236.154; 2.E.236.157; 2.E.236.166; 2.E.236.169; 2.E.236.172;
 20 2.E.236.175; 2.E.236.240; 2.E.236.244; 2.E.237.228; 2.E.237.229; 2.E.237.230;
 2.E.237.231; 2.E.237.236; 2.E.237.237; 2.E.237.238; 2.E.237.239; 2.E.237.154;
 2.E.237.157; 2.E.237.166; 2.E.237.169; 2.E.237.172; 2.E.237.175; 2.E.237.240;
 2.E.237.244; 2.E.238.228; 2.E.238.229; 2.E.238.230; 2.E.238.231; 2.E.238.236;
 2.E.238.237; 2.E.238.238; 2.E.238.239; 2.E.238.154; 2.E.238.157; 2.E.238.166;
 25 2.E.238.169; 2.E.238.172; 2.E.238.175; 2.E.238.240; 2.E.238.244; 2.E.239.228;
 2.E.239.229; 2.E.239.230; 2.E.239.231; 2.E.239.236; 2.E.239.237; 2.E.239.238;
 2.E.239.239; 2.E.239.154; 2.E.239.157; 2.E.239.166; 2.E.239.169; 2.E.239.172;
 2.E.239.175; 2.E.239.240; 2.E.239.244; 2.E.154.228; 2.E.154.229; 2.E.154.230;
 2.E.154.231; 2.E.154.236; 2.E.154.237; 2.E.154.238; 2.E.154.239; 2.E.154.154;
 30 2.E.154.157; 2.E.154.166; 2.E.154.169; 2.E.154.172; 2.E.154.175; 2.E.154.240;
 2.E.154.244; 2.E.157.228; 2.E.157.229; 2.E.157.230; 2.E.157.231; 2.E.157.236;

2.E.157.237; 2.E.157.238; 2.E.157.239; 2.E.157.154; 2.E.157.157; 2.E.157.166;
2.E.157.169; 2.E.157.172; 2.E.157.175; 2.E.157.240; 2.E.157.244; 2.E.166.228;
2.E.166.229; 2.E.166.230; 2.E.166.231; 2.E.166.236; 2.E.166.237; 2.E.166.238;
2.E.166.239; 2.E.166.154; 2.E.166.157; 2.E.166.166; 2.E.166.169; 2.E.166.172;
5 2.E.166.175; 2.E.166.240; 2.E.166.244; 2.E.169.228; 2.E.169.229; 2.E.169.230;
2.E.169.231; 2.E.169.236; 2.E.169.237; 2.E.169.238; 2.E.169.239; 2.E.169.154;
2.E.169.157; 2.E.169.166; 2.E.169.169; 2.E.169.172; 2.E.169.175; 2.E.169.240;
2.E.169.244; 2.E.172.228; 2.E.172.229; 2.E.172.230; 2.E.172.231; 2.E.172.236;
2.E.172.237; 2.E.172.238; 2.E.172.239; 2.E.172.154; 2.E.172.157; 2.E.172.166;
10 2.E.172.169; 2.E.172.172; 2.E.172.175; 2.E.172.240; 2.E.172.244; 2.E.175.228;
2.E.175.229; 2.E.175.230; 2.E.175.231; 2.E.175.236; 2.E.175.237; 2.E.175.238;
2.E.175.239; 2.E.175.154; 2.E.175.157; 2.E.175.166; 2.E.175.169; 2.E.175.172;
2.E.175.175; 2.E.175.240; 2.E.175.244; 2.E.240.228; 2.E.240.229; 2.E.240.230;
2.E.240.231; 2.E.240.236; 2.E.240.237; 2.E.240.238; 2.E.240.239; 2.E.240.154;
15 2.E.240.157; 2.E.240.166; 2.E.240.169; 2.E.240.172; 2.E.240.175; 2.E.240.240;
2.E.240.244; 2.E.244.228; 2.E.244.229; 2.E.244.230; 2.E.244.231; 2.E.244.236;
2.E.244.237; 2.E.244.238; 2.E.244.239; 2.E.244.154; 2.E.244.157; 2.E.244.166;
2.E.244.169; 2.E.244.172; 2.E.244.175; 2.E.244.240; 2.E.244.244;

20 Prodrugs of 2.G

2.G.228.228; 2.G.228.229; 2.G.228.230; 2.G.228.231; 2.G.228.236;
2.G.228.237; 2.G.228.238; 2.G.228.239; 2.G.228.154; 2.G.228.157;
2.G.228.166; 2.G.228.169; 2.G.228.172; 2.G.228.175; 2.G.228.240;
2.G.228.244; 2.G.229.228; 2.G.229.229; 2.G.229.230; 2.G.229.231;
25 2.G.229.236; 2.G.229.237; 2.G.229.238; 2.G.229.239; 2.G.229.154;
2.G.229.157; 2.G.229.166; 2.G.229.169; 2.G.229.172; 2.G.229.175;
2.G.229.240; 2.G.229.244; 2.G.230.228; 2.G.230.229; 2.G.230.230;
2.G.230.231; 2.G.230.236; 2.G.230.237; 2.G.230.238; 2.G.230.239;
2.G.230.154; 2.G.230.157; 2.G.230.166; 2.G.230.169; 2.G.230.172;
30 2.G.230.175; 2.G.230.240; 2.G.230.244; 2.G.231.228; 2.G.231.229;
2.G.231.230; 2.G.231.231; 2.G.231.236; 2.G.231.237; 2.G.231.238;

2.G.231.239; 2.G.231.154; 2.G.231.157; 2.G.231.166; 2.G.231.169;
2.G.231.172; 2.G.231.175; 2.G.231.240; 2.G.231.244; 2.G.236.228;
2.G.236.229; 2.G.236.230; 2.G.236.231; 2.G.236.236; 2.G.236.237;
2.G.236.238; 2.G.236.239; 2.G.236.154; 2.G.236.157; 2.G.236.166;
5 2.G.236.169; 2.G.236.172; 2.G.236.175; 2.G.236.240; 2.G.236.244;
2.G.237.228; 2.G.237.229; 2.G.237.230; 2.G.237.231; 2.G.237.236;
2.G.237.237; 2.G.237.238; 2.G.237.239; 2.G.237.154; 2.G.237.157;
2.G.237.166; 2.G.237.169; 2.G.237.172; 2.G.237.175; 2.G.237.240;
2.G.237.244; 2.G.238.228; 2.G.238.229; 2.G.238.230; 2.G.238.231;
10 2.G.238.236; 2.G.238.237; 2.G.238.238; 2.G.238.239; 2.G.238.154;
2.G.238.157; 2.G.238.166; 2.G.238.169; 2.G.238.172; 2.G.238.175;
2.G.238.240; 2.G.238.244; 2.G.239.228; 2.G.239.229; 2.G.239.230;
2.G.239.231; 2.G.239.236; 2.G.239.237; 2.G.239.238; 2.G.239.239;
2.G.239.154; 2.G.239.157; 2.G.239.166; 2.G.239.169; 2.G.239.172;
15 2.G.239.175; 2.G.239.240; 2.G.239.244; 2.G.154.228; 2.G.154.229;
2.G.154.230; 2.G.154.231; 2.G.154.236; 2.G.154.237; 2.G.154.238;
2.G.154.239; 2.G.154.154; 2.G.154.157; 2.G.154.166; 2.G.154.169;
2.G.154.172; 2.G.154.175; 2.G.154.240; 2.G.154.244; 2.G.157.228;
2.G.157.229; 2.G.157.230; 2.G.157.231; 2.G.157.236; 2.G.157.237;
20 2.G.157.238; 2.G.157.239; 2.G.157.154; 2.G.157.157; 2.G.157.166;
2.G.157.169; 2.G.157.172; 2.G.157.175; 2.G.157.240; 2.G.157.244;
2.G.166.228; 2.G.166.229; 2.G.166.230; 2.G.166.231; 2.G.166.236;
2.G.166.237; 2.G.166.238; 2.G.166.239; 2.G.166.154; 2.G.166.157;
2.G.166.166; 2.G.166.169; 2.G.166.172; 2.G.166.175; 2.G.166.240;
25 2.G.166.244; 2.G.169.228; 2.G.169.229; 2.G.169.230; 2.G.169.231;
2.G.169.236; 2.G.169.237; 2.G.169.238; 2.G.169.239; 2.G.169.154;
2.G.169.157; 2.G.169.166; 2.G.169.169; 2.G.169.172; 2.G.169.175;
2.G.169.240; 2.G.169.244; 2.G.172.228; 2.G.172.229; 2.G.172.230;
2.G.172.231; 2.G.172.236; 2.G.172.237; 2.G.172.238; 2.G.172.239;
30 2.G.172.154; 2.G.172.157; 2.G.172.166; 2.G.172.169; 2.G.172.172;
2.G.172.175; 2.G.172.240; 2.G.172.244; 2.G.175.228; 2.G.175.229;

2.G.175.230; 2.G.175.231; 2.G.175.236; 2.G.175.237; 2.G.175.238;
2.G.175.239; 2.G.175.154; 2.G.175.157; 2.G.175.166; 2.G.175.169;
2.G.175.172; 2.G.175.175; 2.G.175.240; 2.G.175.244; 2.G.240.228;
2.G.240.229; 2.G.240.230; 2.G.240.231; 2.G.240.236; 2.G.240.237;
5 2.G.240.238; 2.G.240.239; 2.G.240.154; 2.G.240.157; 2.G.240.166;
2.G.240.169; 2.G.240.172; 2.G.240.175; 2.G.240.240; 2.G.240.244;
2.G.244.228; 2.G.244.229; 2.G.244.230; 2.G.244.231; 2.G.244.236;
2.G.244.237; 2.G.244.238; 2.G.244.239; 2.G.244.154; 2.G.244.157;
2.G.244.166; 2.G.244.169; 2.G.244.172; 2.G.244.175; 2.G.244.240;
10 2.G.244.244;

Prodrugs of 2.I

2.I.228.228; 2.I.228.229; 2.I.228.230; 2.I.228.231; 2.I.228.236; 2.I.228.237;
2.I.228.238; 2.I.228.239; 2.I.228.154; 2.I.228.157; 2.I.228.166; 2.I.228.169;
15 2.I.228.172; 2.I.228.175; 2.I.228.240; 2.I.228.244; 2.I.229.228; 2.I.229.229;
2.I.229.230; 2.I.229.231; 2.I.229.236; 2.I.229.237; 2.I.229.238; 2.I.229.239;
2.I.229.154; 2.I.229.157; 2.I.229.166; 2.I.229.169; 2.I.229.172; 2.I.229.175;
2.I.229.240; 2.I.229.244; 2.I.230.228; 2.I.230.229; 2.I.230.230; 2.I.230.231;
2.I.230.236; 2.I.230.237; 2.I.230.238; 2.I.230.239; 2.I.230.154; 2.I.230.157;
20 2.I.230.166; 2.I.230.169; 2.I.230.172; 2.I.230.175; 2.I.230.240; 2.I.230.244;
2.I.231.228; 2.I.231.229; 2.I.231.230; 2.I.231.231; 2.I.231.236; 2.I.231.237;
2.I.231.238; 2.I.231.239; 2.I.231.154; 2.I.231.157; 2.I.231.166; 2.I.231.169;
2.I.231.172; 2.I.231.175; 2.I.231.240; 2.I.231.244; 2.I.236.228; 2.I.236.229;
2.I.236.230; 2.I.236.231; 2.I.236.236; 2.I.236.237; 2.I.236.238; 2.I.236.239;
25 2.I.236.154; 2.I.236.157; 2.I.236.166; 2.I.236.169; 2.I.236.172; 2.I.236.175;
2.I.236.240; 2.I.236.244; 2.I.237.228; 2.I.237.229; 2.I.237.230; 2.I.237.231;
2.I.237.236; 2.I.237.237; 2.I.237.238; 2.I.237.239; 2.I.237.154; 2.I.237.157;
2.I.237.166; 2.I.237.169; 2.I.237.172; 2.I.237.175; 2.I.237.240; 2.I.237.244;
2.I.238.228; 2.I.238.229; 2.I.238.230; 2.I.238.231; 2.I.238.236; 2.I.238.237;
30 2.I.238.238; 2.I.238.239; 2.I.238.154; 2.I.238.157; 2.I.238.166; 2.I.238.169;
2.I.238.172; 2.I.238.175; 2.I.238.240; 2.I.238.244; 2.I.239.228; 2.I.239.229;

2.I.239.230; 2.I.239.231; 2.I.239.236; 2.I.239.237; 2.I.239.238; 2.I.239.239;
 2.I.239.154; 2.I.239.157; 2.I.239.166; 2.I.239.169; 2.I.239.172; 2.I.239.175;
 2.I.239.240; 2.I.239.244; 2.I.154.228; 2.I.154.229; 2.I.154.230; 2.I.154.231;
 2.I.154.236; 2.I.154.237; 2.I.154.238; 2.I.154.239; 2.I.154.154; 2.I.154.157;
 5 2.I.154.166; 2.I.154.169; 2.I.154.172; 2.I.154.175; 2.I.154.240; 2.I.154.244;
 2.I.157.228; 2.I.157.229; 2.I.157.230; 2.I.157.231; 2.I.157.236; 2.I.157.237;
 2.I.157.238; 2.I.157.239; 2.I.157.154; 2.I.157.157; 2.I.157.166; 2.I.157.169;
 2.I.157.172; 2.I.157.175; 2.I.157.240; 2.I.157.244; 2.I.166.228; 2.I.166.229;
 2.I.166.230; 2.I.166.231; 2.I.166.236; 2.I.166.237; 2.I.166.238; 2.I.166.239;
 10 2.I.166.154; 2.I.166.157; 2.I.166.166; 2.I.166.169; 2.I.166.172; 2.I.166.175;
 2.I.166.240; 2.I.166.244; 2.I.169.228; 2.I.169.229; 2.I.169.230; 2.I.169.231;
 2.I.169.236; 2.I.169.237; 2.I.169.238; 2.I.169.239; 2.I.169.154; 2.I.169.157;
 2.I.169.166; 2.I.169.169; 2.I.169.172; 2.I.169.175; 2.I.169.240; 2.I.169.244;
 2.I.172.228; 2.I.172.229; 2.I.172.230; 2.I.172.231; 2.I.172.236; 2.I.172.237;
 15 2.I.172.238; 2.I.172.239; 2.I.172.154; 2.I.172.157; 2.I.172.166; 2.I.172.169;
 2.I.172.172; 2.I.172.175; 2.I.172.240; 2.I.172.244; 2.I.175.228; 2.I.175.229;
 2.I.175.230; 2.I.175.231; 2.I.175.236; 2.I.175.237; 2.I.175.238; 2.I.175.239;
 2.I.175.154; 2.I.175.157; 2.I.175.166; 2.I.175.169; 2.I.175.172; 2.I.175.175;
 2.I.175.240; 2.I.175.244; 2.I.240.228; 2.I.240.229; 2.I.240.230; 2.I.240.231;
 20 2.I.240.236; 2.I.240.237; 2.I.240.238; 2.I.240.239; 2.I.240.154; 2.I.240.157;
 2.I.240.166; 2.I.240.169; 2.I.240.172; 2.I.240.175; 2.I.240.240; 2.I.240.244;
 2.I.244.228; 2.I.244.229; 2.I.244.230; 2.I.244.231; 2.I.244.236; 2.I.244.237;
 2.I.244.238; 2.I.244.239; 2.I.244.154; 2.I.244.157; 2.I.244.166; 2.I.244.169;
 2.I.244.172; 2.I.244.175; 2.I.244.240; 2.I.244.244;

25

Prodrugs of 2.I

2.J.228.228; 2.J.228.229; 2.J.228.230; 2.J.228.231; 2.J.228.236; 2.J.228.237;
 2.J.228.238; 2.J.228.239; 2.J.228.154; 2.J.228.157; 2.J.228.166; 2.J.228.169;
 2.J.228.172; 2.J.228.175; 2.J.228.240; 2.J.228.244; 2.J.229.228; 2.J.229.229;
 30 2.J.229.230; 2.J.229.231; 2.J.229.236; 2.J.229.237; 2.J.229.238; 2.J.229.239;
 2.J.229.154; 2.J.229.157; 2.J.229.166; 2.J.229.169; 2.J.229.172; 2.J.229.175;

2.J.229.240; 2.J.229.244; 2.J.230.228; 2.J.230.229; 2.J.230.230; 2.J.230.231;
2.J.230.236; 2.J.230.237; 2.J.230.238; 2.J.230.239; 2.J.230.154; 2.J.230.157;
2.J.230.166; 2.J.230.169; 2.J.230.172; 2.J.230.175; 2.J.230.240; 2.J.230.244;
2.J.231.228; 2.J.231.229; 2.J.231.230; 2.J.231.231; 2.J.231.236; 2.J.231.237;
5 2.J.231.238; 2.J.231.239; 2.J.231.154; 2.J.231.157; 2.J.231.166; 2.J.231.169;
2.J.231.172; 2.J.231.175; 2.J.231.240; 2.J.231.244; 2.J.236.228; 2.J.236.229;
2.J.236.230; 2.J.236.231; 2.J.236.236; 2.J.236.237; 2.J.236.238; 2.J.236.239;
2.J.236.154; 2.J.236.157; 2.J.236.166; 2.J.236.169; 2.J.236.172; 2.J.236.175;
2.J.236.240; 2.J.236.244; 2.J.237.228; 2.J.237.229; 2.J.237.230; 2.J.237.231;
10 2.J.237.236; 2.J.237.237; 2.J.237.238; 2.J.237.239; 2.J.237.154; 2.J.237.157;
2.J.237.166; 2.J.237.169; 2.J.237.172; 2.J.237.175; 2.J.237.240; 2.J.237.244;
2.J.238.228; 2.J.238.229; 2.J.238.230; 2.J.238.231; 2.J.238.236; 2.J.238.237;
2.J.238.238; 2.J.238.239; 2.J.238.154; 2.J.238.157; 2.J.238.166; 2.J.238.169;
2.J.238.172; 2.J.238.175; 2.J.238.240; 2.J.238.244; 2.J.239.228; 2.J.239.229;
15 2.J.239.230; 2.J.239.231; 2.J.239.236; 2.J.239.237; 2.J.239.238; 2.J.239.239;
2.J.239.154; 2.J.239.157; 2.J.239.166; 2.J.239.169; 2.J.239.172; 2.J.239.175;
2.J.239.240; 2.J.239.244; 2.J.154.228; 2.J.154.229; 2.J.154.230; 2.J.154.231;
2.J.154.236; 2.J.154.237; 2.J.154.238; 2.J.154.239; 2.J.154.154; 2.J.154.157;
2.J.154.166; 2.J.154.169; 2.J.154.172; 2.J.154.175; 2.J.154.240; 2.J.154.244;
20 2.J.157.228; 2.J.157.229; 2.J.157.230; 2.J.157.231; 2.J.157.236; 2.J.157.237;
2.J.157.238; 2.J.157.239; 2.J.157.154; 2.J.157.157; 2.J.157.166; 2.J.157.169;
2.J.157.172; 2.J.157.175; 2.J.157.240; 2.J.157.244; 2.J.166.228; 2.J.166.229;
2.J.166.230; 2.J.166.231; 2.J.166.236; 2.J.166.237; 2.J.166.238; 2.J.166.239;
2.J.166.154; 2.J.166.157; 2.J.166.166; 2.J.166.169; 2.J.166.172; 2.J.166.175;
25 2.J.166.240; 2.J.166.244; 2.J.169.228; 2.J.169.229; 2.J.169.230; 2.J.169.231;
2.J.169.236; 2.J.169.237; 2.J.169.238; 2.J.169.239; 2.J.169.154; 2.J.169.157;
2.J.169.166; 2.J.169.169; 2.J.169.172; 2.J.169.175; 2.J.169.240; 2.J.169.244;
2.J.172.228; 2.J.172.229; 2.J.172.230; 2.J.172.231; 2.J.172.236; 2.J.172.237;
2.J.172.238; 2.J.172.239; 2.J.172.154; 2.J.172.157; 2.J.172.166; 2.J.172.169;
30 2.J.172.172; 2.J.172.175; 2.J.172.240; 2.J.172.244; 2.J.175.228; 2.J.175.229;
2.J.175.230; 2.J.175.231; 2.J.175.236; 2.J.175.237; 2.J.175.238; 2.J.175.239;

2.J.175.154; 2.J.175.157; 2.J.175.166; 2.J.175.169; 2.J.175.172; 2.J.175.175;
 2.J.175.240; 2.J.175.244; 2.J.240.228; 2.J.240.229; 2.J.240.230; 2.J.240.231;
 2.J.240.236; 2.J.240.237; 2.J.240.238; 2.J.240.239; 2.J.240.154; 2.J.240.157;
 2.J.240.166; 2.J.240.169; 2.J.240.172; 2.J.240.175; 2.J.240.240; 2.J.240.244;
 5 2.J.244.228; 2.J.244.229; 2.J.244.230; 2.J.244.231; 2.J.244.236; 2.J.244.237;
 2.J.244.238; 2.J.244.239; 2.J.244.154; 2.J.244.157; 2.J.244.166; 2.J.244.169;
 2.J.244.172; 2.J.244.175; 2.J.244.240; 2.J.244.244;

Prodrugs of 2.L

10 2.L.228.228; 2.L.228.229; 2.L.228.230; 2.L.228.231; 2.L.228.236;
 2.L.228.237; 2.L.228.238; 2.L.228.239; 2.L.228.154; 2.L.228.157; 2.L.228.166;
 2.L.228.169; 2.L.228.172; 2.L.228.175; 2.L.228.240; 2.L.228.244; 2.L.229.228;
 2.L.229.229; 2.L.229.230; 2.L.229.231; 2.L.229.236; 2.L.229.237; 2.L.229.238;
 2.L.229.239; 2.L.229.154; 2.L.229.157; 2.L.229.166; 2.L.229.169; 2.L.229.172;
 15 2.L.229.175; 2.L.229.240; 2.L.229.244; 2.L.230.228; 2.L.230.229; 2.L.230.230;
 2.L.230.231; 2.L.230.236; 2.L.230.237; 2.L.230.238; 2.L.230.239; 2.L.230.154;
 2.L.230.157; 2.L.230.166; 2.L.230.169; 2.L.230.172; 2.L.230.175; 2.L.230.240;
 2.L.230.244; 2.L.231.228; 2.L.231.229; 2.L.231.230; 2.L.231.231; 2.L.231.236;
 2.L.231.237; 2.L.231.238; 2.L.231.239; 2.L.231.154; 2.L.231.157; 2.L.231.166;
 20 2.L.231.169; 2.L.231.172; 2.L.231.175; 2.L.231.240; 2.L.231.244; 2.L.236.228;
 2.L.236.229; 2.L.236.230; 2.L.236.231; 2.L.236.236; 2.L.236.237; 2.L.236.238;
 2.L.236.239; 2.L.236.154; 2.L.236.157; 2.L.236.166; 2.L.236.169; 2.L.236.172;
 2.L.236.175; 2.L.236.240; 2.L.236.244; 2.L.237.228; 2.L.237.229; 2.L.237.230;
 2.L.237.231; 2.L.237.236; 2.L.237.237; 2.L.237.238; 2.L.237.239; 2.L.237.154;
 25 2.L.237.157; 2.L.237.166; 2.L.237.169; 2.L.237.172; 2.L.237.175; 2.L.237.240;
 2.L.237.244; 2.L.238.228; 2.L.238.229; 2.L.238.230; 2.L.238.231; 2.L.238.236;
 2.L.238.237; 2.L.238.238; 2.L.238.239; 2.L.238.154; 2.L.238.157; 2.L.238.166;
 2.L.238.169; 2.L.238.172; 2.L.238.175; 2.L.238.240; 2.L.238.244; 2.L.239.228;
 2.L.239.229; 2.L.239.230; 2.L.239.231; 2.L.239.236; 2.L.239.237; 2.L.239.238;
 30 2.L.239.239; 2.L.239.154; 2.L.239.157; 2.L.239.166; 2.L.239.169; 2.L.239.172;
 2.L.239.175; 2.L.239.240; 2.L.239.244; 2.L.154.228; 2.L.154.229; 2.L.154.230;

- 2.L.154.231; 2.L.154.236; 2.L.154.237; 2.L.154.238; 2.L.154.239; 2.L.154.154;
 2.L.154.157; 2.L.154.166; 2.L.154.169; 2.L.154.172; 2.L.154.175; 2.L.154.240;
 2.L.154.244; 2.L.157.228; 2.L.157.229; 2.L.157.230; 2.L.157.231; 2.L.157.236;
 2.L.157.237; 2.L.157.238; 2.L.157.239; 2.L.157.154; 2.L.157.157; 2.L.157.166;
 5 2.L.157.169; 2.L.157.172; 2.L.157.175; 2.L.157.240; 2.L.157.244; 2.L.166.228;
 2.L.166.229; 2.L.166.230; 2.L.166.231; 2.L.166.236; 2.L.166.237; 2.L.166.238;
 2.L.166.239; 2.L.166.154; 2.L.166.157; 2.L.166.166; 2.L.166.169; 2.L.166.172;
 2.L.166.175; 2.L.166.240; 2.L.166.244; 2.L.169.228; 2.L.169.229; 2.L.169.230;
 2.L.169.231; 2.L.169.236; 2.L.169.237; 2.L.169.238; 2.L.169.239; 2.L.169.154;
 10 2.L.169.157; 2.L.169.166; 2.L.169.169; 2.L.169.172; 2.L.169.175; 2.L.169.240;
 2.L.169.244; 2.L.172.228; 2.L.172.229; 2.L.172.230; 2.L.172.231; 2.L.172.236;
 2.L.172.237; 2.L.172.238; 2.L.172.239; 2.L.172.154; 2.L.172.157; 2.L.172.166;
 2.L.172.169; 2.L.172.172; 2.L.172.175; 2.L.172.240; 2.L.172.244; 2.L.175.228;
 2.L.175.229; 2.L.175.230; 2.L.175.231; 2.L.175.236; 2.L.175.237; 2.L.175.238;
 15 2.L.175.239; 2.L.175.154; 2.L.175.157; 2.L.175.166; 2.L.175.169; 2.L.175.172;
 2.L.175.175; 2.L.175.240; 2.L.175.244; 2.L.240.228; 2.L.240.229; 2.L.240.230;
 2.L.240.231; 2.L.240.236; 2.L.240.237; 2.L.240.238; 2.L.240.239; 2.L.240.154;
 2.L.240.157; 2.L.240.166; 2.L.240.169; 2.L.240.172; 2.L.240.175; 2.L.240.240;
 2.L.240.244; 2.L.244.228; 2.L.244.229; 2.L.244.230; 2.L.244.231; 2.L.244.236;
 20 2.L.244.237; 2.L.244.238; 2.L.244.239; 2.L.244.154; 2.L.244.157; 2.L.244.166;
 2.L.244.169; 2.L.244.172; 2.L.244.175; 2.L.244.240; 2.L.244.244;

Prodrugs of 2.O

- 2.O.228.228; 2.O.228.229; 2.O.228.230; 2.O.228.231; 2.O.228.236;
 25 2.O.228.237; 2.O.228.238; 2.O.228.239; 2.O.228.154; 2.O.228.157;
 2.O.228.166; 2.O.228.169; 2.O.228.172; 2.O.228.175; 2.O.228.240;
 2.O.228.244; 2.O.229.228; 2.O.229.229; 2.O.229.230; 2.O.229.231;
 2.O.229.236; 2.O.229.237; 2.O.229.238; 2.O.229.239; 2.O.229.154;
 2.O.229.157; 2.O.229.166; 2.O.229.169; 2.O.229.172; 2.O.229.175;
 30 2.O.229.240; 2.O.229.244; 2.O.230.228; 2.O.230.229; 2.O.230.230;
 2.O.230.231; 2.O.230.236; 2.O.230.237; 2.O.230.238; 2.O.230.239;

2.O.230.154; 2.O.230.157; 2.O.230.166; 2.O.230.169; 2.O.230.172;
2.O.230.175; 2.O.230.240; 2.O.230.244; 2.O.231.228; 2.O.231.229;
2.O.231.230; 2.O.231.231; 2.O.231.236; 2.O.231.237; 2.O.231.238;
2.O.231.239; 2.O.231.154; 2.O.231.157; 2.O.231.166; 2.O.231.169;
5 2.O.231.172; 2.O.231.175; 2.O.231.240; 2.O.231.244; 2.O.236.228;
2.O.236.229; 2.O.236.230; 2.O.236.231; 2.O.236.236; 2.O.236.237;
2.O.236.238; 2.O.236.239; 2.O.236.154; 2.O.236.157; 2.O.236.166;
2.O.236.169; 2.O.236.172; 2.O.236.175; 2.O.236.240; 2.O.236.244;
2.O.237.228; 2.O.237.229; 2.O.237.230; 2.O.237.231; 2.O.237.236;
10 2.O.237.237; 2.O.237.238; 2.O.237.239; 2.O.237.154; 2.O.237.157;
2.O.237.166; 2.O.237.169; 2.O.237.172; 2.O.237.175; 2.O.237.240;
2.O.237.244; 2.O.238.228; 2.O.238.229; 2.O.238.230; 2.O.238.231;
2.O.238.236; 2.O.238.237; 2.O.238.238; 2.O.238.239; 2.O.238.154;
2.O.238.157; 2.O.238.166; 2.O.238.169; 2.O.238.172; 2.O.238.175;
15 2.O.238.240; 2.O.238.244; 2.O.239.228; 2.O.239.229; 2.O.239.230;
2.O.239.231; 2.O.239.236; 2.O.239.237; 2.O.239.238; 2.O.239.239;
2.O.239.154; 2.O.239.157; 2.O.239.166; 2.O.239.169; 2.O.239.172;
2.O.239.175; 2.O.239.240; 2.O.239.244; 2.O.154.228; 2.O.154.229;
2.O.154.230; 2.O.154.231; 2.O.154.236; 2.O.154.237; 2.O.154.238;
20 2.O.154.239; 2.O.154.154; 2.O.154.157; 2.O.154.166; 2.O.154.169;
2.O.154.172; 2.O.154.175; 2.O.154.240; 2.O.154.244; 2.O.157.228;
2.O.157.229; 2.O.157.230; 2.O.157.231; 2.O.157.236; 2.O.157.237;
2.O.157.238; 2.O.157.239; 2.O.157.154; 2.O.157.157; 2.O.157.166;
2.O.157.169; 2.O.157.172; 2.O.157.175; 2.O.157.240; 2.O.157.244;
25 2.O.166.228; 2.O.166.229; 2.O.166.230; 2.O.166.231; 2.O.166.236;
2.O.166.237; 2.O.166.238; 2.O.166.239; 2.O.166.154; 2.O.166.157;
2.O.166.166; 2.O.166.169; 2.O.166.172; 2.O.166.175; 2.O.166.240;
2.O.166.244; 2.O.169.228; 2.O.169.229; 2.O.169.230; 2.O.169.231;
2.O.169.236; 2.O.169.237; 2.O.169.238; 2.O.169.239; 2.O.169.154;
30 2.O.169.157; 2.O.169.166; 2.O.169.169; 2.O.169.172; 2.O.169.175;
2.O.169.240; 2.O.169.244; 2.O.172.228; 2.O.172.229; 2.O.172.230;

2.O.172.231; 2.O.172.236; 2.O.172.237; 2.O.172.238; 2.O.172.239;
 2.O.172.154; 2.O.172.157; 2.O.172.166; 2.O.172.169; 2.O.172.172;
 2.O.172.175; 2.O.172.240; 2.O.172.244; 2.O.175.228; 2.O.175.229;
 2.O.175.230; 2.O.175.231; 2.O.175.236; 2.O.175.237; 2.O.175.238;
 5 2.O.175.239; 2.O.175.154; 2.O.175.157; 2.O.175.166; 2.O.175.169;
 2.O.175.172; 2.O.175.175; 2.O.175.240; 2.O.175.244; 2.O.240.228;
 2.O.240.229; 2.O.240.230; 2.O.240.231; 2.O.240.236; 2.O.240.237;
 2.O.240.238; 2.O.240.239; 2.O.240.154; 2.O.240.157; 2.O.240.166;
 2.O.240.169; 2.O.240.172; 2.O.240.175; 2.O.240.240; 2.O.240.244;
 10 2.O.244.228; 2.O.244.229; 2.O.244.230; 2.O.244.231; 2.O.244.236;
 2.O.244.237; 2.O.244.238; 2.O.244.239; 2.O.244.154; 2.O.244.157;
 2.O.244.166; 2.O.244.169; 2.O.244.172; 2.O.244.175; 2.O.244.240;
 2.O.244.244;

15 Prodrugs of 2.P

2.P.228.228; 2.P.228.229; 2.P.228.230; 2.P.228.231; 2.P.228.236;
 2.P.228.237; 2.P.228.238; 2.P.228.239; 2.P.228.154; 2.P.228.157; 2.P.228.166;
 2.P.228.169; 2.P.228.172; 2.P.228.175; 2.P.228.240; 2.P.228.244; 2.P.229.228;
 2.P.229.229; 2.P.229.230; 2.P.229.231; 2.P.229.236; 2.P.229.237; 2.P.229.238;
 20 2.P.229.239; 2.P.229.154; 2.P.229.157; 2.P.229.166; 2.P.229.169; 2.P.229.172;
 2.P.229.175; 2.P.229.240; 2.P.229.244; 2.P.230.228; 2.P.230.229; 2.P.230.230;
 2.P.230.231; 2.P.230.236; 2.P.230.237; 2.P.230.238; 2.P.230.239; 2.P.230.154;
 2.P.230.157; 2.P.230.166; 2.P.230.169; 2.P.230.172; 2.P.230.175; 2.P.230.240;
 2.P.230.244; 2.P.231.228; 2.P.231.229; 2.P.231.230; 2.P.231.231; 2.P.231.236;
 25 2.P.231.237; 2.P.231.238; 2.P.231.239; 2.P.231.154; 2.P.231.157; 2.P.231.166;
 2.P.231.169; 2.P.231.172; 2.P.231.175; 2.P.231.240; 2.P.231.244; 2.P.236.228;
 2.P.236.229; 2.P.236.230; 2.P.236.231; 2.P.236.236; 2.P.236.237; 2.P.236.238;
 2.P.236.239; 2.P.236.154; 2.P.236.157; 2.P.236.166; 2.P.236.169; 2.P.236.172;
 2.P.236.175; 2.P.236.240; 2.P.236.244; 2.P.237.228; 2.P.237.229; 2.P.237.230;
 30 2.P.237.231; 2.P.237.236; 2.P.237.237; 2.P.237.238; 2.P.237.239; 2.P.237.154;
 2.P.237.157; 2.P.237.166; 2.P.237.169; 2.P.237.172; 2.P.237.175; 2.P.237.240;

- 2.P.237.244; 2.P.238.228; 2.P.238.229; 2.P.238.230; 2.P.238.231; 2.P.238.236;
2.P.238.237; 2.P.238.238; 2.P.238.239; 2.P.238.154; 2.P.238.157; 2.P.238.166;
2.P.238.169; 2.P.238.172; 2.P.238.175; 2.P.238.240; 2.P.238.244; 2.P.239.228;
2.P.239.229; 2.P.239.230; 2.P.239.231; 2.P.239.236; 2.P.239.237; 2.P.239.238;
5 2.P.239.239; 2.P.239.154; 2.P.239.157; 2.P.239.166; 2.P.239.169; 2.P.239.172;
2.P.239.175; 2.P.239.240; 2.P.239.244; 2.P.154.228; 2.P.154.229; 2.P.154.230;
2.P.154.231; 2.P.154.236; 2.P.154.237; 2.P.154.238; 2.P.154.239; 2.P.154.154;
2.P.154.157; 2.P.154.166; 2.P.154.169; 2.P.154.172; 2.P.154.175; 2.P.154.240;
2.P.154.244; 2.P.157.228; 2.P.157.229; 2.P.157.230; 2.P.157.231; 2.P.157.236;
10 2.P.157.237; 2.P.157.238; 2.P.157.239; 2.P.157.154; 2.P.157.157; 2.P.157.166;
2.P.157.169; 2.P.157.172; 2.P.157.175; 2.P.157.240; 2.P.157.244; 2.P.166.228;
2.P.166.229; 2.P.166.230; 2.P.166.231; 2.P.166.236; 2.P.166.237; 2.P.166.238;
2.P.166.239; 2.P.166.154; 2.P.166.157; 2.P.166.166; 2.P.166.169; 2.P.166.172;
2.P.166.175; 2.P.166.240; 2.P.166.244; 2.P.169.228; 2.P.169.229; 2.P.169.230;
15 2.P.169.231; 2.P.169.236; 2.P.169.237; 2.P.169.238; 2.P.169.239; 2.P.169.154;
2.P.169.157; 2.P.169.166; 2.P.169.169; 2.P.169.172; 2.P.169.175; 2.P.169.240;
2.P.169.244; 2.P.172.228; 2.P.172.229; 2.P.172.230; 2.P.172.231; 2.P.172.236;
2.P.172.237; 2.P.172.238; 2.P.172.239; 2.P.172.154; 2.P.172.157; 2.P.172.166;
2.P.172.169; 2.P.172.172; 2.P.172.175; 2.P.172.240; 2.P.172.244; 2.P.175.228;
20 2.P.175.229; 2.P.175.230; 2.P.175.231; 2.P.175.236; 2.P.175.237; 2.P.175.238;
2.P.175.239; 2.P.175.154; 2.P.175.157; 2.P.175.166; 2.P.175.169; 2.P.175.172;
2.P.175.175; 2.P.175.240; 2.P.175.244; 2.P.240.228; 2.P.240.229; 2.P.240.230;
2.P.240.231; 2.P.240.236; 2.P.240.237; 2.P.240.238; 2.P.240.239; 2.P.240.154;
2.P.240.157; 2.P.240.166; 2.P.240.169; 2.P.240.172; 2.P.240.175; 2.P.240.240;
25 2.P.240.244; 2.P.244.228; 2.P.244.229; 2.P.244.230; 2.P.244.231; 2.P.244.236;
2.P.244.237; 2.P.244.238; 2.P.244.239; 2.P.244.154; 2.P.244.157; 2.P.244.166;
2.P.244.169; 2.P.244.172; 2.P.244.175; 2.P.244.240; 2.P.244.244;

Prodrugs of 2.U

- 30 2.U.228.228; 2.U.228.229; 2.U.228.230; 2.U.228.231; 2.U.228.236;
2.U.228.237; 2.U.228.238; 2.U.228.239; 2.U.228.154; 2.U.228.157;

2.U.228.166; 2.U.228.169; 2.U.228.172; 2.U.228.175; 2.U.228.240;
2.U.228.244; 2.U.229.228; 2.U.229.229; 2.U.229.230; 2.U.229.231;
2.U.229.236; 2.U.229.237; 2.U.229.238; 2.U.229.239; 2.U.229.154;
2.U.229.157; 2.U.229.166; 2.U.229.169; 2.U.229.172; 2.U.229.175;
5 2.U.229.240; 2.U.229.244; 2.U.230.228; 2.U.230.229; 2.U.230.230;
2.U.230.231; 2.U.230.236; 2.U.230.237; 2.U.230.238; 2.U.230.239;
2.U.230.154; 2.U.230.157; 2.U.230.166; 2.U.230.169; 2.U.230.172;
2.U.230.175; 2.U.230.240; 2.U.230.244; 2.U.231.228; 2.U.231.229;
2.U.231.230; 2.U.231.231; 2.U.231.236; 2.U.231.237; 2.U.231.238;
10 2.U.231.239; 2.U.231.154; 2.U.231.157; 2.U.231.166; 2.U.231.169;
2.U.231.172; 2.U.231.175; 2.U.231.240; 2.U.231.244; 2.U.236.228;
2.U.236.229; 2.U.236.230; 2.U.236.231; 2.U.236.236; 2.U.236.237;
2.U.236.238; 2.U.236.239; 2.U.236.154; 2.U.236.157; 2.U.236.166;
2.U.236.169; 2.U.236.172; 2.U.236.175; 2.U.236.240; 2.U.236.244;
15 2.U.237.228; 2.U.237.229; 2.U.237.230; 2.U.237.231; 2.U.237.236;
2.U.237.237; 2.U.237.238; 2.U.237.239; 2.U.237.154; 2.U.237.157;
2.U.237.166; 2.U.237.169; 2.U.237.172; 2.U.237.175; 2.U.237.240;
2.U.237.244; 2.U.238.228; 2.U.238.229; 2.U.238.230; 2.U.238.231;
2.U.238.236; 2.U.238.237; 2.U.238.238; 2.U.238.239; 2.U.238.154;
20 2.U.238.157; 2.U.238.166; 2.U.238.169; 2.U.238.172; 2.U.238.175;
2.U.238.240; 2.U.238.244; 2.U.239.228; 2.U.239.229; 2.U.239.230;
2.U.239.231; 2.U.239.236; 2.U.239.237; 2.U.239.238; 2.U.239.239;
2.U.239.154; 2.U.239.157; 2.U.239.166; 2.U.239.169; 2.U.239.172;
2.U.239.175; 2.U.239.240; 2.U.239.244; 2.U.154.228; 2.U.154.229;
25 2.U.154.230; 2.U.154.231; 2.U.154.236; 2.U.154.237; 2.U.154.238;
2.U.154.239; 2.U.154.154; 2.U.154.157; 2.U.154.166; 2.U.154.169;
2.U.154.172; 2.U.154.175; 2.U.154.240; 2.U.154.244; 2.U.157.228;
2.U.157.229; 2.U.157.230; 2.U.157.231; 2.U.157.236; 2.U.157.237;
2.U.157.238; 2.U.157.239; 2.U.157.154; 2.U.157.157; 2.U.157.166;
30 2.U.157.169; 2.U.157.172; 2.U.157.175; 2.U.157.240; 2.U.157.244;
2.U.166.228; 2.U.166.229; 2.U.166.230; 2.U.166.231; 2.U.166.236;

2.U.166.237; 2.U.166.238; 2.U.166.239; 2.U.166.154; 2.U.166.157;
 2.U.166.166; 2.U.166.169; 2.U.166.172; 2.U.166.175; 2.U.166.240;
 2.U.166.244; 2.U.169.228; 2.U.169.229; 2.U.169.230; 2.U.169.231;
 2.U.169.236; 2.U.169.237; 2.U.169.238; 2.U.169.239; 2.U.169.154;
 5 2.U.169.157; 2.U.169.166; 2.U.169.169; 2.U.169.172; 2.U.169.175;
 2.U.169.240; 2.U.169.244; 2.U.172.228; 2.U.172.229; 2.U.172.230;
 2.U.172.231; 2.U.172.236; 2.U.172.237; 2.U.172.238; 2.U.172.239;
 2.U.172.154; 2.U.172.157; 2.U.172.166; 2.U.172.169; 2.U.172.172;
 2.U.172.175; 2.U.172.240; 2.U.172.244; 2.U.175.228; 2.U.175.229;
 10 2.U.175.230; 2.U.175.231; 2.U.175.236; 2.U.175.237; 2.U.175.238;
 2.U.175.239; 2.U.175.154; 2.U.175.157; 2.U.175.166; 2.U.175.169;
 2.U.175.172; 2.U.175.175; 2.U.175.240; 2.U.175.244; 2.U.240.228;
 2.U.240.229; 2.U.240.230; 2.U.240.231; 2.U.240.236; 2.U.240.237;
 2.U.240.238; 2.U.240.239; 2.U.240.154; 2.U.240.157; 2.U.240.166;
 15 2.U.240.169; 2.U.240.172; 2.U.240.175; 2.U.240.240; 2.U.240.244;
 2.U.244.228; 2.U.244.229; 2.U.244.230; 2.U.244.231; 2.U.244.236;
 2.U.244.237; 2.U.244.238; 2.U.244.239; 2.U.244.154; 2.U.244.157;
 2.U.244.166; 2.U.244.169; 2.U.244.172; 2.U.244.175; 2.U.244.240;
 2.U.244.244;

20

Prodrugs of 2.W

2.W.228.228; 2.W.228.229; 2.W.228.230; 2.W.228.231; 2.W.228.236;
 2.W.228.237; 2.W.228.238; 2.W.228.239; 2.W.228.154; 2.W.228.157;
 2.W.228.166; 2.W.228.169; 2.W.228.172; 2.W.228.175; 2.W.228.240;
 25 2.W.228.244; 2.W.229.228; 2.W.229.229; 2.W.229.230; 2.W.229.231;
 2.W.229.236; 2.W.229.237; 2.W.229.238; 2.W.229.239; 2.W.229.154;
 2.W.229.157; 2.W.229.166; 2.W.229.169; 2.W.229.172; 2.W.229.175;
 2.W.229.240; 2.W.229.244; 2.W.230.228; 2.W.230.229; 2.W.230.230;
 2.W.230.231; 2.W.230.236; 2.W.230.237; 2.W.230.238; 2.W.230.239;
 30 2.W.230.154; 2.W.230.157; 2.W.230.166; 2.W.230.169; 2.W.230.172;
 2.W.230.175; 2.W.230.240; 2.W.230.244; 2.W.231.228; 2.W.231.229;

2.W.231.230; 2.W.231.231; 2.W.231.236; 2.W.231.237; 2.W.231.238;
2.W.231.239; 2.W.231.154; 2.W.231.157; 2.W.231.166; 2.W.231.169;
2.W.231.172; 2.W.231.175; 2.W.231.240; 2.W.231.244; 2.W.236.228;
2.W.236.229; 2.W.236.230; 2.W.236.231; 2.W.236.236; 2.W.236.237;
5 2.W.236.238; 2.W.236.239; 2.W.236.154; 2.W.236.157; 2.W.236.166;
2.W.236.169; 2.W.236.172; 2.W.236.175; 2.W.236.240; 2.W.236.244;
2.W.237.228; 2.W.237.229; 2.W.237.230; 2.W.237.231; 2.W.237.236;
2.W.237.237; 2.W.237.238; 2.W.237.239; 2.W.237.154; 2.W.237.157;
2.W.237.166; 2.W.237.169; 2.W.237.172; 2.W.237.175; 2.W.237.240;
10 2.W.237.244; 2.W.238.228; 2.W.238.229; 2.W.238.230; 2.W.238.231;
2.W.238.236; 2.W.238.237; 2.W.238.238; 2.W.238.239; 2.W.238.154;
2.W.238.157; 2.W.238.166; 2.W.238.169; 2.W.238.172; 2.W.238.175;
2.W.238.240; 2.W.238.244; 2.W.239.228; 2.W.239.229; 2.W.239.230;
2.W.239.231; 2.W.239.236; 2.W.239.237; 2.W.239.238; 2.W.239.239;
15 2.W.239.154; 2.W.239.157; 2.W.239.166; 2.W.239.169; 2.W.239.172;
2.W.239.175; 2.W.239.240; 2.W.239.244; 2.W.154.228; 2.W.154.229;
2.W.154.230; 2.W.154.231; 2.W.154.236; 2.W.154.237; 2.W.154.238;
2.W.154.239; 2.W.154.154; 2.W.154.157; 2.W.154.166; 2.W.154.169;
2.W.154.172; 2.W.154.175; 2.W.154.240; 2.W.154.244; 2.W.157.228;
20 2.W.157.229; 2.W.157.230; 2.W.157.231; 2.W.157.236; 2.W.157.237;
2.W.157.238; 2.W.157.239; 2.W.157.154; 2.W.157.157; 2.W.157.166;
2.W.157.169; 2.W.157.172; 2.W.157.175; 2.W.157.240; 2.W.157.244;
2.W.166.228; 2.W.166.229; 2.W.166.230; 2.W.166.231; 2.W.166.236;
2.W.166.237; 2.W.166.238; 2.W.166.239; 2.W.166.154; 2.W.166.157;
25 2.W.166.166; 2.W.166.169; 2.W.166.172; 2.W.166.175; 2.W.166.240;
2.W.166.244; 2.W.169.228; 2.W.169.229; 2.W.169.230; 2.W.169.231;
2.W.169.236; 2.W.169.237; 2.W.169.238; 2.W.169.239; 2.W.169.154;
2.W.169.157; 2.W.169.166; 2.W.169.169; 2.W.169.172; 2.W.169.175;
2.W.169.240; 2.W.169.244; 2.W.172.228; 2.W.172.229; 2.W.172.230;
30 2.W.172.231; 2.W.172.236; 2.W.172.237; 2.W.172.238; 2.W.172.239;
2.W.172.154; 2.W.172.157; 2.W.172.166; 2.W.172.169; 2.W.172.172;

2.W.172.175; 2.W.172.240; 2.W.172.244; 2.W.175.228; 2.W.175.229;
 2.W.175.230; 2.W.175.231; 2.W.175.236; 2.W.175.237; 2.W.175.238;
 2.W.175.239; 2.W.175.154; 2.W.175.157; 2.W.175.166; 2.W.175.169;
 2.W.175.172; 2.W.175.175; 2.W.175.240; 2.W.175.244; 2.W.240.228;
 5 2.W.240.229; 2.W.240.230; 2.W.240.231; 2.W.240.236; 2.W.240.237;
 2.W.240.238; 2.W.240.239; 2.W.240.154; 2.W.240.157; 2.W.240.166;
 2.W.240.169; 2.W.240.172; 2.W.240.175; 2.W.240.240; 2.W.240.244;
 2.W.244.228; 2.W.244.229; 2.W.244.230; 2.W.244.231; 2.W.244.236;
 2.W.244.237; 2.W.244.238; 2.W.244.239; 2.W.244.154; 2.W.244.157;
 10 2.W.244.166; 2.W.244.169; 2.W.244.172; 2.W.244.175; 2.W.244.240;
 2.W.244.244;

Prodrugs of 2.Y

2.Y.228.228; 2.Y.228.229; 2.Y.228.230; 2.Y.228.231; 2.Y.228.236;
 15 2.Y.228.237; 2.Y.228.238; 2.Y.228.239; 2.Y.228.154; 2.Y.228.157; 2.Y.228.166;
 2.Y.228.169; 2.Y.228.172; 2.Y.228.175; 2.Y.228.240; 2.Y.228.244; 2.Y.229.228;
 2.Y.229.229; 2.Y.229.230; 2.Y.229.231; 2.Y.229.236; 2.Y.229.237; 2.Y.229.238;
 2.Y.229.239; 2.Y.229.154; 2.Y.229.157; 2.Y.229.166; 2.Y.229.169; 2.Y.229.172;
 2.Y.229.175; 2.Y.229.240; 2.Y.229.244; 2.Y.230.228; 2.Y.230.229; 2.Y.230.230;
 20 2.Y.230.231; 2.Y.230.236; 2.Y.230.237; 2.Y.230.238; 2.Y.230.239; 2.Y.230.154;
 2.Y.230.157; 2.Y.230.166; 2.Y.230.169; 2.Y.230.172; 2.Y.230.175; 2.Y.230.240;
 2.Y.230.244; 2.Y.231.228; 2.Y.231.229; 2.Y.231.230; 2.Y.231.231; 2.Y.231.236;
 2.Y.231.237; 2.Y.231.238; 2.Y.231.239; 2.Y.231.154; 2.Y.231.157; 2.Y.231.166;
 2.Y.231.169; 2.Y.231.172; 2.Y.231.175; 2.Y.231.240; 2.Y.231.244; 2.Y.236.228;
 25 2.Y.236.229; 2.Y.236.230; 2.Y.236.231; 2.Y.236.236; 2.Y.236.237; 2.Y.236.238;
 2.Y.236.239; 2.Y.236.154; 2.Y.236.157; 2.Y.236.166; 2.Y.236.169; 2.Y.236.172;
 2.Y.236.175; 2.Y.236.240; 2.Y.236.244; 2.Y.237.228; 2.Y.237.229; 2.Y.237.230;
 2.Y.237.231; 2.Y.237.236; 2.Y.237.237; 2.Y.237.238; 2.Y.237.239; 2.Y.237.154;
 2.Y.237.157; 2.Y.237.166; 2.Y.237.169; 2.Y.237.172; 2.Y.237.175; 2.Y.237.240;
 30 2.Y.237.244; 2.Y.238.228; 2.Y.238.229; 2.Y.238.230; 2.Y.238.231; 2.Y.238.236;
 2.Y.238.237; 2.Y.238.238; 2.Y.238.239; 2.Y.238.154; 2.Y.238.157; 2.Y.238.166;

- 2.Y.238.169; 2.Y.238.172; 2.Y.238.175; 2.Y.238.240; 2.Y.238.244; 2.Y.239.228;
 2.Y.239.229; 2.Y.239.230; 2.Y.239.231; 2.Y.239.236; 2.Y.239.237; 2.Y.239.238;
 2.Y.239.239; 2.Y.239.154; 2.Y.239.157; 2.Y.239.166; 2.Y.239.169; 2.Y.239.172;
 2.Y.239.175; 2.Y.239.240; 2.Y.239.244; 2.Y.154.228; 2.Y.154.229; 2.Y.154.230;
 5 2.Y.154.231; 2.Y.154.236; 2.Y.154.237; 2.Y.154.238; 2.Y.154.239; 2.Y.154.154;
 2.Y.154.157; 2.Y.154.166; 2.Y.154.169; 2.Y.154.172; 2.Y.154.175; 2.Y.154.240;
 2.Y.154.244; 2.Y.157.228; 2.Y.157.229; 2.Y.157.230; 2.Y.157.231; 2.Y.157.236;
 2.Y.157.237; 2.Y.157.238; 2.Y.157.239; 2.Y.157.154; 2.Y.157.157; 2.Y.157.166;
 2.Y.157.169; 2.Y.157.172; 2.Y.157.175; 2.Y.157.240; 2.Y.157.244; 2.Y.166.228;
 10 2.Y.166.229; 2.Y.166.230; 2.Y.166.231; 2.Y.166.236; 2.Y.166.237; 2.Y.166.238;
 2.Y.166.239; 2.Y.166.154; 2.Y.166.157; 2.Y.166.166; 2.Y.166.169; 2.Y.166.172;
 2.Y.166.175; 2.Y.166.240; 2.Y.166.244; 2.Y.169.228; 2.Y.169.229; 2.Y.169.230;
 2.Y.169.231; 2.Y.169.236; 2.Y.169.237; 2.Y.169.238; 2.Y.169.239; 2.Y.169.154;
 2.Y.169.157; 2.Y.169.166; 2.Y.169.169; 2.Y.169.172; 2.Y.169.175; 2.Y.169.240;
 15 2.Y.169.244; 2.Y.172.228; 2.Y.172.229; 2.Y.172.230; 2.Y.172.231; 2.Y.172.236;
 2.Y.172.237; 2.Y.172.238; 2.Y.172.239; 2.Y.172.154; 2.Y.172.157; 2.Y.172.166;
 2.Y.172.169; 2.Y.172.172; 2.Y.172.175; 2.Y.172.240; 2.Y.172.244; 2.Y.175.228;
 2.Y.175.229; 2.Y.175.230; 2.Y.175.231; 2.Y.175.236; 2.Y.175.237; 2.Y.175.238;
 2.Y.175.239; 2.Y.175.154; 2.Y.175.157; 2.Y.175.166; 2.Y.175.169; 2.Y.175.172;
 20 2.Y.175.175; 2.Y.175.240; 2.Y.175.244; 2.Y.240.228; 2.Y.240.229; 2.Y.240.230;
 2.Y.240.231; 2.Y.240.236; 2.Y.240.237; 2.Y.240.238; 2.Y.240.239; 2.Y.240.154;
 2.Y.240.157; 2.Y.240.166; 2.Y.240.169; 2.Y.240.172; 2.Y.240.175; 2.Y.240.240;
 2.Y.240.244; 2.Y.244.228; 2.Y.244.229; 2.Y.244.230; 2.Y.244.231; 2.Y.244.236;
 2.Y.244.237; 2.Y.244.238; 2.Y.244.239; 2.Y.244.154; 2.Y.244.157; 2.Y.244.166;
 25 2.Y.244.169; 2.Y.244.172; 2.Y.244.175; 2.Y.244.240; 2.Y.244.244;

Prodrugs of 3.B

- 3.B.228.228; 3.B.228.229; 3.B.228.230; 3.B.228.231; 3.B.228.236;
 3.B.228.237; 3.B.228.238; 3.B.228.239; 3.B.228.154; 3.B.228.157; 3.B.228.166;
 30 3.B.228.169; 3.B.228.172; 3.B.228.175; 3.B.228.240; 3.B.228.244; 3.B.229.228;
 3.B.229.229; 3.B.229.230; 3.B.229.231; 3.B.229.236; 3.B.229.237; 3.B.229.238;

3.B.229.239; 3.B.229.154; 3.B.229.157; 3.B.229.166; 3.B.229.169; 3.B.229.172;
 3.B.229.175; 3.B.229.240; 3.B.229.244; 3.B.230.228; 3.B.230.229; 3.B.230.230;
 3.B.230.231; 3.B.230.236; 3.B.230.237; 3.B.230.238; 3.B.230.239; 3.B.230.154;
 3.B.230.157; 3.B.230.166; 3.B.230.169; 3.B.230.172; 3.B.230.175; 3.B.230.240;
 5 3.B.230.244; 3.B.231.228; 3.B.231.229; 3.B.231.230; 3.B.231.231; 3.B.231.236;
 3.B.231.237; 3.B.231.238; 3.B.231.239; 3.B.231.154; 3.B.231.157; 3.B.231.166;
 3.B.231.169; 3.B.231.172; 3.B.231.175; 3.B.231.240; 3.B.231.244; 3.B.236.228;
 3.B.236.229; 3.B.236.230; 3.B.236.231; 3.B.236.236; 3.B.236.237; 3.B.236.238;
 3.B.236.239; 3.B.236.154; 3.B.236.157; 3.B.236.166; 3.B.236.169; 3.B.236.172;
 10 3.B.236.175; 3.B.236.240; 3.B.236.244; 3.B.237.228; 3.B.237.229; 3.B.237.230;
 3.B.237.231; 3.B.237.236; 3.B.237.237; 3.B.237.238; 3.B.237.239; 3.B.237.154;
 3.B.237.157; 3.B.237.166; 3.B.237.169; 3.B.237.172; 3.B.237.175; 3.B.237.240;
 3.B.237.244; 3.B.238.228; 3.B.238.229; 3.B.238.230; 3.B.238.231; 3.B.238.236;
 3.B.238.237; 3.B.238.238; 3.B.238.239; 3.B.238.154; 3.B.238.157; 3.B.238.166;
 15 3.B.238.169; 3.B.238.172; 3.B.238.175; 3.B.238.240; 3.B.238.244; 3.B.239.228;
 3.B.239.229; 3.B.239.230; 3.B.239.231; 3.B.239.236; 3.B.239.237; 3.B.239.238;
 3.B.239.239; 3.B.239.154; 3.B.239.157; 3.B.239.166; 3.B.239.169; 3.B.239.172;
 3.B.239.175; 3.B.239.240; 3.B.239.244; 3.B.154.228; 3.B.154.229; 3.B.154.230;
 3.B.154.231; 3.B.154.236; 3.B.154.237; 3.B.154.238; 3.B.154.239; 3.B.154.154;
 20 3.B.154.157; 3.B.154.166; 3.B.154.169; 3.B.154.172; 3.B.154.175; 3.B.154.240;
 3.B.154.244; 3.B.157.228; 3.B.157.229; 3.B.157.230; 3.B.157.231; 3.B.157.236;
 3.B.157.237; 3.B.157.238; 3.B.157.239; 3.B.157.154; 3.B.157.157; 3.B.157.166;
 3.B.157.169; 3.B.157.172; 3.B.157.175; 3.B.157.240; 3.B.157.244; 3.B.166.228;
 3.B.166.229; 3.B.166.230; 3.B.166.231; 3.B.166.236; 3.B.166.237; 3.B.166.238;
 25 3.B.166.239; 3.B.166.154; 3.B.166.157; 3.B.166.166; 3.B.166.169; 3.B.166.172;
 3.B.166.175; 3.B.166.240; 3.B.166.244; 3.B.169.228; 3.B.169.229; 3.B.169.230;
 3.B.169.231; 3.B.169.236; 3.B.169.237; 3.B.169.238; 3.B.169.239; 3.B.169.154;
 3.B.169.157; 3.B.169.166; 3.B.169.169; 3.B.169.172; 3.B.169.175; 3.B.169.240;
 3.B.169.244; 3.B.172.228; 3.B.172.229; 3.B.172.230; 3.B.172.231; 3.B.172.236;
 30 3.B.172.237; 3.B.172.238; 3.B.172.239; 3.B.172.154; 3.B.172.157; 3.B.172.166;
 3.B.172.169; 3.B.172.172; 3.B.172.175; 3.B.172.240; 3.B.172.244; 3.B.175.228;

3.B.175.229; 3.B.175.230; 3.B.175.231; 3.B.175.236; 3.B.175.237; 3.B.175.238;
 3.B.175.239; 3.B.175.154; 3.B.175.157; 3.B.175.166; 3.B.175.169; 3.B.175.172;
 3.B.175.175; 3.B.175.240; 3.B.175.244; 3.B.240.228; 3.B.240.229; 3.B.240.230;
 3.B.240.231; 3.B.240.236; 3.B.240.237; 3.B.240.238; 3.B.240.239; 3.B.240.154;
 5 3.B.240.157; 3.B.240.166; 3.B.240.169; 3.B.240.172; 3.B.240.175; 3.B.240.240;
 3.B.240.244; 3.B.244.228; 3.B.244.229; 3.B.244.230; 3.B.244.231; 3.B.244.236;
 3.B.244.237; 3.B.244.238; 3.B.244.239; 3.B.244.154; 3.B.244.157; 3.B.244.166;
 3.B.244.169; 3.B.244.172; 3.B.244.175; 3.B.244.240; 3.B.244.244;

10 Prodrugs of 3.D

3.D.228.228; 3.D.228.229; 3.D.228.230; 3.D.228.231; 3.D.228.236;
 3.D.228.237; 3.D.228.238; 3.D.228.239; 3.D.228.154; 3.D.228.157;
 3.D.228.166; 3.D.228.169; 3.D.228.172; 3.D.228.175; 3.D.228.240;
 3.D.228.244; 3.D.229.228; 3.D.229.229; 3.D.229.230; 3.D.229.231;
 15 3.D.229.236; 3.D.229.237; 3.D.229.238; 3.D.229.239; 3.D.229.154;
 3.D.229.157; 3.D.229.166; 3.D.229.169; 3.D.229.172; 3.D.229.175;
 3.D.229.240; 3.D.229.244; 3.D.230.228; 3.D.230.229; 3.D.230.230;
 3.D.230.231; 3.D.230.236; 3.D.230.237; 3.D.230.238; 3.D.230.239;
 3.D.230.154; 3.D.230.157; 3.D.230.166; 3.D.230.169; 3.D.230.172;
 20 3.D.230.175; 3.D.230.240; 3.D.230.244; 3.D.231.228; 3.D.231.229;
 3.D.231.230; 3.D.231.231; 3.D.231.236; 3.D.231.237; 3.D.231.238;
 3.D.231.239; 3.D.231.154; 3.D.231.157; 3.D.231.166; 3.D.231.169;
 3.D.231.172; 3.D.231.175; 3.D.231.240; 3.D.231.244; 3.D.236.228;
 3.D.236.229; 3.D.236.230; 3.D.236.231; 3.D.236.236; 3.D.236.237;
 25 3.D.236.238; 3.D.236.239; 3.D.236.154; 3.D.236.157; 3.D.236.166;
 3.D.236.169; 3.D.236.172; 3.D.236.175; 3.D.236.240; 3.D.236.244;
 3.D.237.228; 3.D.237.229; 3.D.237.230; 3.D.237.231; 3.D.237.236;
 3.D.237.237; 3.D.237.238; 3.D.237.239; 3.D.237.154; 3.D.237.157;
 3.D.237.166; 3.D.237.169; 3.D.237.172; 3.D.237.175; 3.D.237.240;
 30 3.D.237.244; 3.D.238.228; 3.D.238.229; 3.D.238.230; 3.D.238.231;
 3.D.238.236; 3.D.238.237; 3.D.238.238; 3.D.238.239; 3.D.238.154;

3.D.238.157; 3.D.238.166; 3.D.238.169; 3.D.238.172; 3.D.238.175;
3.D.238.240; 3.D.238.244; 3.D.239.228; 3.D.239.229; 3.D.239.230;
3.D.239.231; 3.D.239.236; 3.D.239.237; 3.D.239.238; 3.D.239.239;
3.D.239.154; 3.D.239.157; 3.D.239.166; 3.D.239.169; 3.D.239.172;
5 3.D.239.175; 3.D.239.240; 3.D.239.244; 3.D.154.228; 3.D.154.229;
3.D.154.230; 3.D.154.231; 3.D.154.236; 3.D.154.237; 3.D.154.238;
3.D.154.239; 3.D.154.154; 3.D.154.157; 3.D.154.166; 3.D.154.169;
3.D.154.172; 3.D.154.175; 3.D.154.240; 3.D.154.244; 3.D.157.228;
3.D.157.229; 3.D.157.230; 3.D.157.231; 3.D.157.236; 3.D.157.237;
10 3.D.157.238; 3.D.157.239; 3.D.157.154; 3.D.157.157; 3.D.157.166;
3.D.157.169; 3.D.157.172; 3.D.157.175; 3.D.157.240; 3.D.157.244;
3.D.166.228; 3.D.166.229; 3.D.166.230; 3.D.166.231; 3.D.166.236;
3.D.166.237; 3.D.166.238; 3.D.166.239; 3.D.166.154; 3.D.166.157;
3.D.166.166; 3.D.166.169; 3.D.166.172; 3.D.166.175; 3.D.166.240;
15 3.D.166.244; 3.D.169.228; 3.D.169.229; 3.D.169.230; 3.D.169.231;
3.D.169.236; 3.D.169.237; 3.D.169.238; 3.D.169.239; 3.D.169.154;
3.D.169.157; 3.D.169.166; 3.D.169.169; 3.D.169.172; 3.D.169.175;
3.D.169.240; 3.D.169.244; 3.D.172.228; 3.D.172.229; 3.D.172.230;
3.D.172.231; 3.D.172.236; 3.D.172.237; 3.D.172.238; 3.D.172.239;
20 3.D.172.154; 3.D.172.157; 3.D.172.166; 3.D.172.169; 3.D.172.172;
3.D.172.175; 3.D.172.240; 3.D.172.244; 3.D.175.228; 3.D.175.229;
3.D.175.230; 3.D.175.231; 3.D.175.236; 3.D.175.237; 3.D.175.238;
3.D.175.239; 3.D.175.154; 3.D.175.157; 3.D.175.166; 3.D.175.169;
3.D.175.172; 3.D.175.175; 3.D.175.240; 3.D.175.244; 3.D.240.228;
25 3.D.240.229; 3.D.240.230; 3.D.240.231; 3.D.240.236; 3.D.240.237;
3.D.240.238; 3.D.240.239; 3.D.240.154; 3.D.240.157; 3.D.240.166;
3.D.240.169; 3.D.240.172; 3.D.240.175; 3.D.240.240; 3.D.240.244;
3.D.244.228; 3.D.244.229; 3.D.244.230; 3.D.244.231; 3.D.244.236;
3.D.244.237; 3.D.244.238; 3.D.244.239; 3.D.244.154; 3.D.244.157;
30 3.D.244.166; 3.D.244.169; 3.D.244.172; 3.D.244.175; 3.D.244.240;
3.D.244.244;

Prodrugs of 3.E

- 3.E.228.228; 3.E.228.229; 3.E.228.230; 3.E.228.231; 3.E.228.236;
3.E.228.237; 3.E.228.238; 3.E.228.239; 3.E.228.154; 3.E.228.157; 3.E.228.166;
5 3.E.228.169; 3.E.228.172; 3.E.228.175; 3.E.228.240; 3.E.228.244; 3.E.229.228;
3.E.229.229; 3.E.229.230; 3.E.229.231; 3.E.229.236; 3.E.229.237; 3.E.229.238;
3.E.229.239; 3.E.229.154; 3.E.229.157; 3.E.229.166; 3.E.229.169; 3.E.229.172;
3.E.229.175; 3.E.229.240; 3.E.229.244; 3.E.230.228; 3.E.230.229; 3.E.230.230;
3.E.230.231; 3.E.230.236; 3.E.230.237; 3.E.230.238; 3.E.230.239; 3.E.230.154;
10 3.E.230.157; 3.E.230.166; 3.E.230.169; 3.E.230.172; 3.E.230.175; 3.E.230.240;
3.E.230.244; 3.E.231.228; 3.E.231.229; 3.E.231.230; 3.E.231.231; 3.E.231.236;
3.E.231.237; 3.E.231.238; 3.E.231.239; 3.E.231.154; 3.E.231.157; 3.E.231.166;
3.E.231.169; 3.E.231.172; 3.E.231.175; 3.E.231.240; 3.E.231.244; 3.E.236.228;
3.E.236.229; 3.E.236.230; 3.E.236.231; 3.E.236.236; 3.E.236.237; 3.E.236.238;
15 3.E.236.239; 3.E.236.154; 3.E.236.157; 3.E.236.166; 3.E.236.169; 3.E.236.172;
3.E.236.175; 3.E.236.240; 3.E.236.244; 3.E.237.228; 3.E.237.229; 3.E.237.230;
3.E.237.231; 3.E.237.236; 3.E.237.237; 3.E.237.238; 3.E.237.239; 3.E.237.154;
3.E.237.157; 3.E.237.166; 3.E.237.169; 3.E.237.172; 3.E.237.175; 3.E.237.240;
3.E.237.244; 3.E.238.228; 3.E.238.229; 3.E.238.230; 3.E.238.231; 3.E.238.236;
20 3.E.238.237; 3.E.238.238; 3.E.238.239; 3.E.238.154; 3.E.238.157; 3.E.238.166;
3.E.238.169; 3.E.238.172; 3.E.238.175; 3.E.238.240; 3.E.238.244; 3.E.239.228;
3.E.239.229; 3.E.239.230; 3.E.239.231; 3.E.239.236; 3.E.239.237; 3.E.239.238;
3.E.239.239; 3.E.239.154; 3.E.239.157; 3.E.239.166; 3.E.239.169; 3.E.239.172;
3.E.239.175; 3.E.239.240; 3.E.239.244; 3.E.154.228; 3.E.154.229; 3.E.154.230;
25 3.E.154.231; 3.E.154.236; 3.E.154.237; 3.E.154.238; 3.E.154.239; 3.E.154.154;
3.E.154.157; 3.E.154.166; 3.E.154.169; 3.E.154.172; 3.E.154.175; 3.E.154.240;
3.E.154.244; 3.E.157.228; 3.E.157.229; 3.E.157.230; 3.E.157.231; 3.E.157.236;
3.E.157.237; 3.E.157.238; 3.E.157.239; 3.E.157.154; 3.E.157.157; 3.E.157.166;
3.E.157.169; 3.E.157.172; 3.E.157.175; 3.E.157.240; 3.E.157.244; 3.E.166.228;
30 3.E.166.229; 3.E.166.230; 3.E.166.231; 3.E.166.236; 3.E.166.237; 3.E.166.238;
3.E.166.239; 3.E.166.154; 3.E.166.157; 3.E.166.166; 3.E.166.169; 3.E.166.172;

3.E.166.175; 3.E.166.240; 3.E.166.244; 3.E.169.228; 3.E.169.229; 3.E.169.230;
3.E.169.231; 3.E.169.236; 3.E.169.237; 3.E.169.238; 3.E.169.239; 3.E.169.154;
3.E.169.157; 3.E.169.166; 3.E.169.169; 3.E.169.172; 3.E.169.175; 3.E.169.240;
3.E.169.244; 3.E.172.228; 3.E.172.229; 3.E.172.230; 3.E.172.231; 3.E.172.236;
5 3.E.172.237; 3.E.172.238; 3.E.172.239; 3.E.172.154; 3.E.172.157; 3.E.172.166;
3.E.172.169; 3.E.172.172; 3.E.172.175; 3.E.172.240; 3.E.172.244; 3.E.175.228;
3.E.175.229; 3.E.175.230; 3.E.175.231; 3.E.175.236; 3.E.175.237; 3.E.175.238;
3.E.175.239; 3.E.175.154; 3.E.175.157; 3.E.175.166; 3.E.175.169; 3.E.175.172;
3.E.175.175; 3.E.175.240; 3.E.175.244; 3.E.240.228; 3.E.240.229; 3.E.240.230;
10 3.E.240.231; 3.E.240.236; 3.E.240.237; 3.E.240.238; 3.E.240.239; 3.E.240.154;
3.E.240.157; 3.E.240.166; 3.E.240.169; 3.E.240.172; 3.E.240.175; 3.E.240.240;
3.E.240.244; 3.E.244.228; 3.E.244.229; 3.E.244.230; 3.E.244.231; 3.E.244.236;
3.E.244.237; 3.E.244.238; 3.E.244.239; 3.E.244.154; 3.E.244.157; 3.E.244.166;
3.E.244.169; 3.E.244.172; 3.E.244.175; 3.E.244.240; 3.E.244.244;

15

Prodrugs of 3.G

3.G.228.228; 3.G.228.229; 3.G.228.230; 3.G.228.231; 3.G.228.236;
3.G.228.237; 3.G.228.238; 3.G.228.239; 3.G.228.154; 3.G.228.157;
3.G.228.166; 3.G.228.169; 3.G.228.172; 3.G.228.175; 3.G.228.240;
20 3.G.228.244; 3.G.229.228; 3.G.229.229; 3.G.229.230; 3.G.229.231;
3.G.229.236; 3.G.229.237; 3.G.229.238; 3.G.229.239; 3.G.229.154;
3.G.229.157; 3.G.229.166; 3.G.229.169; 3.G.229.172; 3.G.229.175;
3.G.229.240; 3.G.229.244; 3.G.230.228; 3.G.230.229; 3.G.230.230;
3.G.230.231; 3.G.230.236; 3.G.230.237; 3.G.230.238; 3.G.230.239;
25 3.G.230.154; 3.G.230.157; 3.G.230.166; 3.G.230.169; 3.G.230.172;
3.G.230.175; 3.G.230.240; 3.G.230.244; 3.G.231.228; 3.G.231.229;
3.G.231.230; 3.G.231.231; 3.G.231.236; 3.G.231.237; 3.G.231.238;
3.G.231.239; 3.G.231.154; 3.G.231.157; 3.G.231.166; 3.G.231.169;
3.G.231.172; 3.G.231.175; 3.G.231.240; 3.G.231.244; 3.G.236.228;
30 3.G.236.229; 3.G.236.230; 3.G.236.231; 3.G.236.236; 3.G.236.237;
3.G.236.238; 3.G.236.239; 3.G.236.154; 3.G.236.157; 3.G.236.166;

- 3.G.236.169; 3.G.236.172; 3.G.236.175; 3.G.236.240; 3.G.236.244;
3.G.237.228; 3.G.237.229; 3.G.237.230; 3.G.237.231; 3.G.237.236;
3.G.237.237; 3.G.237.238; 3.G.237.239; 3.G.237.154; 3.G.237.157;
3.G.237.166; 3.G.237.169; 3.G.237.172; 3.G.237.175; 3.G.237.240;
5 3.G.237.244; 3.G.238.228; 3.G.238.229; 3.G.238.230; 3.G.238.231;
3.G.238.236; 3.G.238.237; 3.G.238.238; 3.G.238.239; 3.G.238.154;
3.G.238.157; 3.G.238.166; 3.G.238.169; 3.G.238.172; 3.G.238.175;
3.G.238.240; 3.G.238.244; 3.G.239.228; 3.G.239.229; 3.G.239.230;
3.G.239.231; 3.G.239.236; 3.G.239.237; 3.G.239.238; 3.G.239.239;
10 3.G.239.154; 3.G.239.157; 3.G.239.166; 3.G.239.169; 3.G.239.172;
3.G.239.175; 3.G.239.240; 3.G.239.244; 3.G.154.228; 3.G.154.229;
3.G.154.230; 3.G.154.231; 3.G.154.236; 3.G.154.237; 3.G.154.238;
3.G.154.239; 3.G.154.154; 3.G.154.157; 3.G.154.166; 3.G.154.169;
3.G.154.172; 3.G.154.175; 3.G.154.240; 3.G.154.244; 3.G.157.228;
15 3.G.157.229; 3.G.157.230; 3.G.157.231; 3.G.157.236; 3.G.157.237;
3.G.157.238; 3.G.157.239; 3.G.157.154; 3.G.157.157; 3.G.157.166;
3.G.157.169; 3.G.157.172; 3.G.157.175; 3.G.157.240; 3.G.157.244;
3.G.166.228; 3.G.166.229; 3.G.166.230; 3.G.166.231; 3.G.166.236;
3.G.166.237; 3.G.166.238; 3.G.166.239; 3.G.166.154; 3.G.166.157;
20 3.G.166.166; 3.G.166.169; 3.G.166.172; 3.G.166.175; 3.G.166.240;
3.G.166.244; 3.G.169.228; 3.G.169.229; 3.G.169.230; 3.G.169.231;
3.G.169.236; 3.G.169.237; 3.G.169.238; 3.G.169.239; 3.G.169.154;
3.G.169.157; 3.G.169.166; 3.G.169.169; 3.G.169.172; 3.G.169.175;
3.G.169.240; 3.G.169.244; 3.G.172.228; 3.G.172.229; 3.G.172.230;
25 3.G.172.231; 3.G.172.236; 3.G.172.237; 3.G.172.238; 3.G.172.239;
3.G.172.154; 3.G.172.157; 3.G.172.166; 3.G.172.169; 3.G.172.172;
3.G.172.175; 3.G.172.240; 3.G.172.244; 3.G.175.228; 3.G.175.229;
3.G.175.230; 3.G.175.231; 3.G.175.236; 3.G.175.237; 3.G.175.238;
3.G.175.239; 3.G.175.154; 3.G.175.157; 3.G.175.166; 3.G.175.169;
30 3.G.175.172; 3.G.175.175; 3.G.175.240; 3.G.175.244; 3.G.240.228;
3.G.240.229; 3.G.240.230; 3.G.240.231; 3.G.240.236; 3.G.240.237;

3.G.240.238; 3.G.240.239; 3.G.240.154; 3.G.240.157; 3.G.240.166;
3.G.240.169; 3.G.240.172; 3.G.240.175; 3.G.240.240; 3.G.240.244;
3.G.244.228; 3.G.244.229; 3.G.244.230; 3.G.244.231; 3.G.244.236;
3.G.244.237; 3.G.244.238; 3.G.244.239; 3.G.244.154; 3.G.244.157;
5 3.G.244.166; 3.G.244.169; 3.G.244.172; 3.G.244.175; 3.G.244.240;
3.G.244.244;

Prodrugs of 3.I

3.I.228.228; 3.I.228.229; 3.I.228.230; 3.I.228.231; 3.I.228.236; 3.I.228.237;
10 3.I.228.238; 3.I.228.239; 3.I.228.154; 3.I.228.157; 3.I.228.166; 3.I.228.169;
3.I.228.172; 3.I.228.175; 3.I.228.240; 3.I.228.244; 3.I.229.228; 3.I.229.229;
3.I.229.230; 3.I.229.231; 3.I.229.236; 3.I.229.237; 3.I.229.238; 3.I.229.239;
3.I.229.154; 3.I.229.157; 3.I.229.166; 3.I.229.169; 3.I.229.172; 3.I.229.175;
3.I.229.240; 3.I.229.244; 3.I.230.228; 3.I.230.229; 3.I.230.230; 3.I.230.231;
15 3.I.230.236; 3.I.230.237; 3.I.230.238; 3.I.230.239; 3.I.230.154; 3.I.230.157;
3.I.230.166; 3.I.230.169; 3.I.230.172; 3.I.230.175; 3.I.230.240; 3.I.230.244;
3.I.231.228; 3.I.231.229; 3.I.231.230; 3.I.231.231; 3.I.231.236; 3.I.231.237;
3.I.231.238; 3.I.231.239; 3.I.231.154; 3.I.231.157; 3.I.231.166; 3.I.231.169;
3.I.231.172; 3.I.231.175; 3.I.231.240; 3.I.231.244; 3.I.236.228; 3.I.236.229;
20 3.I.236.230; 3.I.236.231; 3.I.236.236; 3.I.236.237; 3.I.236.238; 3.I.236.239;
3.I.236.154; 3.I.236.157; 3.I.236.166; 3.I.236.169; 3.I.236.172; 3.I.236.175;
3.I.236.240; 3.I.236.244; 3.I.237.228; 3.I.237.229; 3.I.237.230; 3.I.237.231;
3.I.237.236; 3.I.237.237; 3.I.237.238; 3.I.237.239; 3.I.237.154; 3.I.237.157;
3.I.237.166; 3.I.237.169; 3.I.237.172; 3.I.237.175; 3.I.237.240; 3.I.237.244;
25 3.I.238.228; 3.I.238.229; 3.I.238.230; 3.I.238.231; 3.I.238.236; 3.I.238.237;
3.I.238.238; 3.I.238.239; 3.I.238.154; 3.I.238.157; 3.I.238.166; 3.I.238.169;
3.I.238.172; 3.I.238.175; 3.I.238.240; 3.I.238.244; 3.I.239.228; 3.I.239.229;
3.I.239.230; 3.I.239.231; 3.I.239.236; 3.I.239.237; 3.I.239.238; 3.I.239.239;
3.I.239.154; 3.I.239.157; 3.I.239.166; 3.I.239.169; 3.I.239.172; 3.I.239.175;
30 3.I.239.240; 3.I.239.244; 3.I.154.228; 3.I.154.229; 3.I.154.230; 3.I.154.231;
3.I.154.236; 3.I.154.237; 3.I.154.238; 3.I.154.239; 3.I.154.154; 3.I.154.157;

- 3.I.154.166; 3.I.154.169; 3.I.154.172; 3.I.154.175; 3.I.154.240; 3.I.154.244;
 3.I.157.228; 3.I.157.229; 3.I.157.230; 3.I.157.231; 3.I.157.236; 3.I.157.237;
 3.I.157.238; 3.I.157.239; 3.I.157.154; 3.I.157.157; 3.I.157.166; 3.I.157.169;
 3.I.157.172; 3.I.157.175; 3.I.157.240; 3.I.157.244; 3.I.166.228; 3.I.166.229;
 5 3.I.166.230; 3.I.166.231; 3.I.166.236; 3.I.166.237; 3.I.166.238; 3.I.166.239;
 3.I.166.154; 3.I.166.157; 3.I.166.166; 3.I.166.169; 3.I.166.172; 3.I.166.175;
 3.I.166.240; 3.I.166.244; 3.I.169.228; 3.I.169.229; 3.I.169.230; 3.I.169.231;
 3.I.169.236; 3.I.169.237; 3.I.169.238; 3.I.169.239; 3.I.169.154; 3.I.169.157;
 3.I.169.166; 3.I.169.169; 3.I.169.172; 3.I.169.175; 3.I.169.240; 3.I.169.244;
 10 3.I.172.228; 3.I.172.229; 3.I.172.230; 3.I.172.231; 3.I.172.236; 3.I.172.237;
 3.I.172.238; 3.I.172.239; 3.I.172.154; 3.I.172.157; 3.I.172.166; 3.I.172.169;
 3.I.172.172; 3.I.172.175; 3.I.172.240; 3.I.172.244; 3.I.175.228; 3.I.175.229;
 3.I.175.230; 3.I.175.231; 3.I.175.236; 3.I.175.237; 3.I.175.238; 3.I.175.239;
 3.I.175.154; 3.I.175.157; 3.I.175.166; 3.I.175.169; 3.I.175.172; 3.I.175.175;
 15 3.I.175.240; 3.I.175.244; 3.I.240.228; 3.I.240.229; 3.I.240.230; 3.I.240.231;
 3.I.240.236; 3.I.240.237; 3.I.240.238; 3.I.240.239; 3.I.240.154; 3.I.240.157;
 3.I.240.166; 3.I.240.169; 3.I.240.172; 3.I.240.175; 3.I.240.240; 3.I.240.244;
 3.I.244.228; 3.I.244.229; 3.I.244.230; 3.I.244.231; 3.I.244.236; 3.I.244.237;
 3.I.244.238; 3.I.244.239; 3.I.244.154; 3.I.244.157; 3.I.244.166; 3.I.244.169;
 20 3.I.244.172; 3.I.244.175; 3.I.244.240; 3.I.244.244;

Prodrugs of 3.J

- 3.J.228.228; 3.J.228.229; 3.J.228.230; 3.J.228.231; 3.J.228.236; 3.J.228.237;
 3.J.228.238; 3.J.228.239; 3.J.228.154; 3.J.228.157; 3.J.228.166; 3.J.228.169;
 25 3.J.228.172; 3.J.228.175; 3.J.228.240; 3.J.228.244; 3.J.229.228; 3.J.229.229;
 3.J.229.230; 3.J.229.231; 3.J.229.236; 3.J.229.237; 3.J.229.238; 3.J.229.239;
 3.J.229.154; 3.J.229.157; 3.J.229.166; 3.J.229.169; 3.J.229.172; 3.J.229.175;
 3.J.229.240; 3.J.229.244; 3.J.230.228; 3.J.230.229; 3.J.230.230; 3.J.230.231;
 3.J.230.236; 3.J.230.237; 3.J.230.238; 3.J.230.239; 3.J.230.154; 3.J.230.157;
 30 3.J.230.166; 3.J.230.169; 3.J.230.172; 3.J.230.175; 3.J.230.240; 3.J.230.244;
 3.J.231.228; 3.J.231.229; 3.J.231.230; 3.J.231.231; 3.J.231.236; 3.J.231.237;

3.J.231.238; 3.J.231.239; 3.J.231.154; 3.J.231.157; 3.J.231.166; 3.J.231.169;
3.J.231.172; 3.J.231.175; 3.J.231.240; 3.J.231.244; 3.J.236.228; 3.J.236.229;
3.J.236.230; 3.J.236.231; 3.J.236.236; 3.J.236.237; 3.J.236.238; 3.J.236.239;
3.J.236.154; 3.J.236.157; 3.J.236.166; 3.J.236.169; 3.J.236.172; 3.J.236.175;
5 3.J.236.240; 3.J.236.244; 3.J.237.228; 3.J.237.229; 3.J.237.230; 3.J.237.231;
3.J.237.236; 3.J.237.237; 3.J.237.238; 3.J.237.239; 3.J.237.154; 3.J.237.157;
3.J.237.166; 3.J.237.169; 3.J.237.172; 3.J.237.175; 3.J.237.240; 3.J.237.244;
3.J.238.228; 3.J.238.229; 3.J.238.230; 3.J.238.231; 3.J.238.236; 3.J.238.237;
3.J.238.238; 3.J.238.239; 3.J.238.154; 3.J.238.157; 3.J.238.166; 3.J.238.169;
10 3.J.238.172; 3.J.238.175; 3.J.238.240; 3.J.238.244; 3.J.239.228; 3.J.239.229;
3.J.239.230; 3.J.239.231; 3.J.239.236; 3.J.239.237; 3.J.239.238; 3.J.239.239;
3.J.239.154; 3.J.239.157; 3.J.239.166; 3.J.239.169; 3.J.239.172; 3.J.239.175;
3.J.239.240; 3.J.239.244; 3.J.154.228; 3.J.154.229; 3.J.154.230; 3.J.154.231;
3.J.154.236; 3.J.154.237; 3.J.154.238; 3.J.154.239; 3.J.154.154; 3.J.154.157;
15 3.J.154.166; 3.J.154.169; 3.J.154.172; 3.J.154.175; 3.J.154.240; 3.J.154.244;
3.J.157.228; 3.J.157.229; 3.J.157.230; 3.J.157.231; 3.J.157.236; 3.J.157.237;
3.J.157.238; 3.J.157.239; 3.J.157.154; 3.J.157.157; 3.J.157.166; 3.J.157.169;
3.J.157.172; 3.J.157.175; 3.J.157.240; 3.J.157.244; 3.J.166.228; 3.J.166.229;
3.J.166.230; 3.J.166.231; 3.J.166.236; 3.J.166.237; 3.J.166.238; 3.J.166.239;
20 3.J.166.154; 3.J.166.157; 3.J.166.166; 3.J.166.169; 3.J.166.172; 3.J.166.175;
3.J.166.240; 3.J.166.244; 3.J.169.228; 3.J.169.229; 3.J.169.230; 3.J.169.231;
3.J.169.236; 3.J.169.237; 3.J.169.238; 3.J.169.239; 3.J.169.154; 3.J.169.157;
3.J.169.166; 3.J.169.169; 3.J.169.172; 3.J.169.175; 3.J.169.240; 3.J.169.244;
3.J.172.228; 3.J.172.229; 3.J.172.230; 3.J.172.231; 3.J.172.236; 3.J.172.237;
25 3.J.172.238; 3.J.172.239; 3.J.172.154; 3.J.172.157; 3.J.172.166; 3.J.172.169;
3.J.172.172; 3.J.172.175; 3.J.172.240; 3.J.172.244; 3.J.175.228; 3.J.175.229;
3.J.175.230; 3.J.175.231; 3.J.175.236; 3.J.175.237; 3.J.175.238; 3.J.175.239;
3.J.175.154; 3.J.175.157; 3.J.175.166; 3.J.175.169; 3.J.175.172; 3.J.175.175;
3.J.175.240; 3.J.175.244; 3.J.240.228; 3.J.240.229; 3.J.240.230; 3.J.240.231;
30 3.J.240.236; 3.J.240.237; 3.J.240.238; 3.J.240.239; 3.J.240.154; 3.J.240.157;
3.J.240.166; 3.J.240.169; 3.J.240.172; 3.J.240.175; 3.J.240.240; 3.J.240.244;

3.J.244.228; 3.J.244.229; 3.J.244.230; 3.J.244.231; 3.J.244.236; 3.J.244.237;
3.J.244.238; 3.J.244.239; 3.J.244.154; 3.J.244.157; 3.J.244.166; 3.J.244.169;
3.J.244.172; 3.J.244.175; 3.J.244.240; 3.J.244.244;

5 Prodrugs of 3.L

- 3.L.228.228; 3.L.228.229; 3.L.228.230; 3.L.228.231; 3.L.228.236;
3.L.228.237; 3.L.228.238; 3.L.228.239; 3.L.228.154; 3.L.228.157; 3.L.228.166;
3.L.228.169; 3.L.228.172; 3.L.228.175; 3.L.228.240; 3.L.228.244; 3.L.229.228;
3.L.229.229; 3.L.229.230; 3.L.229.231; 3.L.229.236; 3.L.229.237; 3.L.229.238;
10 3.L.229.239; 3.L.229.154; 3.L.229.157; 3.L.229.166; 3.L.229.169; 3.L.229.172;
3.L.229.175; 3.L.229.240; 3.L.229.244; 3.L.230.228; 3.L.230.229; 3.L.230.230;
3.L.230.231; 3.L.230.236; 3.L.230.237; 3.L.230.238; 3.L.230.239; 3.L.230.154;
3.L.230.157; 3.L.230.166; 3.L.230.169; 3.L.230.172; 3.L.230.175; 3.L.230.240;
3.L.230.244; 3.L.231.228; 3.L.231.229; 3.L.231.230; 3.L.231.231; 3.L.231.236;
15 3.L.231.237; 3.L.231.238; 3.L.231.239; 3.L.231.154; 3.L.231.157; 3.L.231.166;
3.L.231.169; 3.L.231.172; 3.L.231.175; 3.L.231.240; 3.L.231.244; 3.L.236.228;
3.L.236.229; 3.L.236.230; 3.L.236.231; 3.L.236.236; 3.L.236.237; 3.L.236.238;
3.L.236.239; 3.L.236.154; 3.L.236.157; 3.L.236.166; 3.L.236.169; 3.L.236.172;
3.L.236.175; 3.L.236.240; 3.L.236.244; 3.L.237.228; 3.L.237.229; 3.L.237.230;
20 3.L.237.231; 3.L.237.236; 3.L.237.237; 3.L.237.238; 3.L.237.239; 3.L.237.154;
3.L.237.157; 3.L.237.166; 3.L.237.169; 3.L.237.172; 3.L.237.175; 3.L.237.240;
3.L.237.244; 3.L.238.228; 3.L.238.229; 3.L.238.230; 3.L.238.231; 3.L.238.236;
3.L.238.237; 3.L.238.238; 3.L.238.239; 3.L.238.154; 3.L.238.157; 3.L.238.166;
3.L.238.169; 3.L.238.172; 3.L.238.175; 3.L.238.240; 3.L.238.244; 3.L.239.228;
25 3.L.239.229; 3.L.239.230; 3.L.239.231; 3.L.239.236; 3.L.239.237; 3.L.239.238;
3.L.239.239; 3.L.239.154; 3.L.239.157; 3.L.239.166; 3.L.239.169; 3.L.239.172;
3.L.239.175; 3.L.239.240; 3.L.239.244; 3.L.154.228; 3.L.154.229; 3.L.154.230;
3.L.154.231; 3.L.154.236; 3.L.154.237; 3.L.154.238; 3.L.154.239; 3.L.154.154;
3.L.154.157; 3.L.154.166; 3.L.154.169; 3.L.154.172; 3.L.154.175; 3.L.154.240;
30 3.L.154.244; 3.L.157.228; 3.L.157.229; 3.L.157.230; 3.L.157.231; 3.L.157.236;
3.L.157.237; 3.L.157.238; 3.L.157.239; 3.L.157.154; 3.L.157.157; 3.L.157.166;

3.L.157.169; 3.L.157.172; 3.L.157.175; 3.L.157.240; 3.L.157.244; 3.L.166.228;
3.L.166.229; 3.L.166.230; 3.L.166.231; 3.L.166.236; 3.L.166.237; 3.L.166.238;
3.L.166.239; 3.L.166.154; 3.L.166.157; 3.L.166.166; 3.L.166.169; 3.L.166.172;
3.L.166.175; 3.L.166.240; 3.L.166.244; 3.L.169.228; 3.L.169.229; 3.L.169.230;
5 3.L.169.231; 3.L.169.236; 3.L.169.237; 3.L.169.238; 3.L.169.239; 3.L.169.154;
3.L.169.157; 3.L.169.166; 3.L.169.169; 3.L.169.172; 3.L.169.175; 3.L.169.240;
3.L.169.244; 3.L.172.228; 3.L.172.229; 3.L.172.230; 3.L.172.231; 3.L.172.236;
3.L.172.237; 3.L.172.238; 3.L.172.239; 3.L.172.154; 3.L.172.157; 3.L.172.166;
3.L.172.169; 3.L.172.172; 3.L.172.175; 3.L.172.240; 3.L.172.244; 3.L.175.228;
10 3.L.175.229; 3.L.175.230; 3.L.175.231; 3.L.175.236; 3.L.175.237; 3.L.175.238;
3.L.175.239; 3.L.175.154; 3.L.175.157; 3.L.175.166; 3.L.175.169; 3.L.175.172;
3.L.175.175; 3.L.175.240; 3.L.175.244; 3.L.240.228; 3.L.240.229; 3.L.240.230;
3.L.240.231; 3.L.240.236; 3.L.240.237; 3.L.240.238; 3.L.240.239; 3.L.240.154;
3.L.240.157; 3.L.240.166; 3.L.240.169; 3.L.240.172; 3.L.240.175; 3.L.240.240;
15 3.L.240.244; 3.L.244.228; 3.L.244.229; 3.L.244.230; 3.L.244.231; 3.L.244.236;
3.L.244.237; 3.L.244.238; 3.L.244.239; 3.L.244.154; 3.L.244.157; 3.L.244.166;
3.L.244.169; 3.L.244.172; 3.L.244.175; 3.L.244.240; 3.L.244.244;

Prodrugs of 3.O

20 3.O.228.228; 3.O.228.229; 3.O.228.230; 3.O.228.231; 3.O.228.236;
3.O.228.237; 3.O.228.238; 3.O.228.239; 3.O.228.154; 3.O.228.157;
3.O.228.166; 3.O.228.169; 3.O.228.172; 3.O.228.175; 3.O.228.240;
3.O.228.244; 3.O.229.228; 3.O.229.229; 3.O.229.230; 3.O.229.231;
3.O.229.236; 3.O.229.237; 3.O.229.238; 3.O.229.239; 3.O.229.154;
25 3.O.229.157; 3.O.229.166; 3.O.229.169; 3.O.229.172; 3.O.229.175;
3.O.229.240; 3.O.229.244; 3.O.230.228; 3.O.230.229; 3.O.230.230;
3.O.230.231; 3.O.230.236; 3.O.230.237; 3.O.230.238; 3.O.230.239;
3.O.230.154; 3.O.230.157; 3.O.230.166; 3.O.230.169; 3.O.230.172;
3.O.230.175; 3.O.230.240; 3.O.230.244; 3.O.231.228; 3.O.231.229;
30 3.O.231.230; 3.O.231.231; 3.O.231.236; 3.O.231.237; 3.O.231.238;
3.O.231.239; 3.O.231.154; 3.O.231.157; 3.O.231.166; 3.O.231.169;

3.O.231.172; 3.O.231.175; 3.O.231.240; 3.O.231.244; 3.O.236.228;
3.O.236.229; 3.O.236.230; 3.O.236.231; 3.O.236.236; 3.O.236.237;
3.O.236.238; 3.O.236.239; 3.O.236.154; 3.O.236.157; 3.O.236.166;
3.O.236.169; 3.O.236.172; 3.O.236.175; 3.O.236.240; 3.O.236.244;
5 3.O.237.228; 3.O.237.229; 3.O.237.230; 3.O.237.231; 3.O.237.236;
3.O.237.237; 3.O.237.238; 3.O.237.239; 3.O.237.154; 3.O.237.157;
3.O.237.166; 3.O.237.169; 3.O.237.172; 3.O.237.175; 3.O.237.240;
3.O.237.244; 3.O.238.228; 3.O.238.229; 3.O.238.230; 3.O.238.231;
3.O.238.236; 3.O.238.237; 3.O.238.238; 3.O.238.239; 3.O.238.154;
10 3.O.238.157; 3.O.238.166; 3.O.238.169; 3.O.238.172; 3.O.238.175;
3.O.238.240; 3.O.238.244; 3.O.239.228; 3.O.239.229; 3.O.239.230;
3.O.239.231; 3.O.239.236; 3.O.239.237; 3.O.239.238; 3.O.239.239;
3.O.239.154; 3.O.239.157; 3.O.239.166; 3.O.239.169; 3.O.239.172;
3.O.239.175; 3.O.239.240; 3.O.239.244; 3.O.154.228; 3.O.154.229;
15 3.O.154.230; 3.O.154.231; 3.O.154.236; 3.O.154.237; 3.O.154.238;
3.O.154.239; 3.O.154.154; 3.O.154.157; 3.O.154.166; 3.O.154.169;
3.O.154.172; 3.O.154.175; 3.O.154.240; 3.O.154.244; 3.O.157.228;
3.O.157.229; 3.O.157.230; 3.O.157.231; 3.O.157.236; 3.O.157.237;
3.O.157.238; 3.O.157.239; 3.O.157.154; 3.O.157.157; 3.O.157.166;
20 3.O.157.169; 3.O.157.172; 3.O.157.175; 3.O.157.240; 3.O.157.244;
3.O.166.228; 3.O.166.229; 3.O.166.230; 3.O.166.231; 3.O.166.236;
3.O.166.237; 3.O.166.238; 3.O.166.239; 3.O.166.154; 3.O.166.157;
3.O.166.166; 3.O.166.169; 3.O.166.172; 3.O.166.175; 3.O.166.240;
3.O.166.244; 3.O.169.228; 3.O.169.229; 3.O.169.230; 3.O.169.231;
25 3.O.169.236; 3.O.169.237; 3.O.169.238; 3.O.169.239; 3.O.169.154;
3.O.169.157; 3.O.169.166; 3.O.169.169; 3.O.169.172; 3.O.169.175;
3.O.169.240; 3.O.169.244; 3.O.172.228; 3.O.172.229; 3.O.172.230;
3.O.172.231; 3.O.172.236; 3.O.172.237; 3.O.172.238; 3.O.172.239;
3.O.172.154; 3.O.172.157; 3.O.172.166; 3.O.172.169; 3.O.172.172;
30 3.O.172.175; 3.O.172.240; 3.O.172.244; 3.O.175.228; 3.O.175.229;
3.O.175.230; 3.O.175.231; 3.O.175.236; 3.O.175.237; 3.O.175.238;

3.O.175.239; 3.O.175.154; 3.O.175.157; 3.O.175.166; 3.O.175.169;
3.O.175.172; 3.O.175.175; 3.O.175.240; 3.O.175.244; 3.O.240.228;
3.O.240.229; 3.O.240.230; 3.O.240.231; 3.O.240.236; 3.O.240.237;
3.O.240.238; 3.O.240.239; 3.O.240.154; 3.O.240.157; 3.O.240.166;
5 3.O.240.169; 3.O.240.172; 3.O.240.175; 3.O.240.240; 3.O.240.244;
3.O.244.228; 3.O.244.229; 3.O.244.230; 3.O.244.231; 3.O.244.236;
3.O.244.237; 3.O.244.238; 3.O.244.239; 3.O.244.154; 3.O.244.157;
3.O.244.166; 3.O.244.169; 3.O.244.172; 3.O.244.175; 3.O.244.240;
3.O.244.244;

10

Prodrugs of 3.P

3.P.228.228; 3.P.228.229; 3.P.228.230; 3.P.228.231; 3.P.228.236;
3.P.228.237; 3.P.228.238; 3.P.228.239; 3.P.228.154; 3.P.228.157; 3.P.228.166;
3.P.228.169; 3.P.228.172; 3.P.228.175; 3.P.228.240; 3.P.228.244; 3.P.229.228;
15 3.P.229.229; 3.P.229.230; 3.P.229.231; 3.P.229.236; 3.P.229.237; 3.P.229.238;
3.P.229.239; 3.P.229.154; 3.P.229.157; 3.P.229.166; 3.P.229.169; 3.P.229.172;
3.P.229.175; 3.P.229.240; 3.P.229.244; 3.P.230.228; 3.P.230.229; 3.P.230.230;
3.P.230.231; 3.P.230.236; 3.P.230.237; 3.P.230.238; 3.P.230.239; 3.P.230.154;
3.P.230.157; 3.P.230.166; 3.P.230.169; 3.P.230.172; 3.P.230.175; 3.P.230.240;
20 3.P.230.244; 3.P.231.228; 3.P.231.229; 3.P.231.230; 3.P.231.231; 3.P.231.236;
3.P.231.237; 3.P.231.238; 3.P.231.239; 3.P.231.154; 3.P.231.157; 3.P.231.166;
3.P.231.169; 3.P.231.172; 3.P.231.175; 3.P.231.240; 3.P.231.244; 3.P.236.228;
3.P.236.229; 3.P.236.230; 3.P.236.231; 3.P.236.236; 3.P.236.237; 3.P.236.238;
3.P.236.239; 3.P.236.154; 3.P.236.157; 3.P.236.166; 3.P.236.169; 3.P.236.172;
25 3.P.236.175; 3.P.236.240; 3.P.236.244; 3.P.237.228; 3.P.237.229; 3.P.237.230;
3.P.237.231; 3.P.237.236; 3.P.237.237; 3.P.237.238; 3.P.237.239; 3.P.237.154;
3.P.237.157; 3.P.237.166; 3.P.237.169; 3.P.237.172; 3.P.237.175; 3.P.237.240;
3.P.237.244; 3.P.238.228; 3.P.238.229; 3.P.238.230; 3.P.238.231; 3.P.238.236;
3.P.238.237; 3.P.238.238; 3.P.238.239; 3.P.238.154; 3.P.238.157; 3.P.238.166;
30 3.P.238.169; 3.P.238.172; 3.P.238.175; 3.P.238.240; 3.P.238.244; 3.P.239.228;
3.P.239.229; 3.P.239.230; 3.P.239.231; 3.P.239.236; 3.P.239.237; 3.P.239.238;

3.P.239.239; 3.P.239.154; 3.P.239.157; 3.P.239.166; 3.P.239.169; 3.P.239.172;
 3.P.239.175; 3.P.239.240; 3.P.239.244; 3.P.154.228; 3.P.154.229; 3.P.154.230;
 3.P.154.231; 3.P.154.236; 3.P.154.237; 3.P.154.238; 3.P.154.239; 3.P.154.154;
 3.P.154.157; 3.P.154.166; 3.P.154.169; 3.P.154.172; 3.P.154.175; 3.P.154.240;
 5 3.P.154.244; 3.P.157.228; 3.P.157.229; 3.P.157.230; 3.P.157.231; 3.P.157.236;
 3.P.157.237; 3.P.157.238; 3.P.157.239; 3.P.157.154; 3.P.157.157; 3.P.157.166;
 3.P.157.169; 3.P.157.172; 3.P.157.175; 3.P.157.240; 3.P.157.244; 3.P.166.228;
 3.P.166.229; 3.P.166.230; 3.P.166.231; 3.P.166.236; 3.P.166.237; 3.P.166.238;
 3.P.166.239; 3.P.166.154; 3.P.166.157; 3.P.166.166; 3.P.166.169; 3.P.166.172;
 10 3.P.166.175; 3.P.166.240; 3.P.166.244; 3.P.169.228; 3.P.169.229; 3.P.169.230;
 3.P.169.231; 3.P.169.236; 3.P.169.237; 3.P.169.238; 3.P.169.239; 3.P.169.154;
 3.P.169.157; 3.P.169.166; 3.P.169.169; 3.P.169.172; 3.P.169.175; 3.P.169.240;
 3.P.169.244; 3.P.172.228; 3.P.172.229; 3.P.172.230; 3.P.172.231; 3.P.172.236;
 3.P.172.237; 3.P.172.238; 3.P.172.239; 3.P.172.154; 3.P.172.157; 3.P.172.166;
 15 3.P.172.169; 3.P.172.172; 3.P.172.175; 3.P.172.240; 3.P.172.244; 3.P.175.228;
 3.P.175.229; 3.P.175.230; 3.P.175.231; 3.P.175.236; 3.P.175.237; 3.P.175.238;
 3.P.175.239; 3.P.175.154; 3.P.175.157; 3.P.175.166; 3.P.175.169; 3.P.175.172;
 3.P.175.175; 3.P.175.240; 3.P.175.244; 3.P.240.228; 3.P.240.229; 3.P.240.230;
 3.P.240.231; 3.P.240.236; 3.P.240.237; 3.P.240.238; 3.P.240.239; 3.P.240.154;
 20 3.P.240.157; 3.P.240.166; 3.P.240.169; 3.P.240.172; 3.P.240.175; 3.P.240.240;
 3.P.240.244; 3.P.244.228; 3.P.244.229; 3.P.244.230; 3.P.244.231; 3.P.244.236;
 3.P.244.237; 3.P.244.238; 3.P.244.239; 3.P.244.154; 3.P.244.157; 3.P.244.166;
 3.P.244.169; 3.P.244.172; 3.P.244.175; 3.P.244.240; 3.P.244.244;

25 Prodrugs of 3.U

3.U.228.228; 3.U.228.229; 3.U.228.230; 3.U.228.231; 3.U.228.236;
 3.U.228.237; 3.U.228.238; 3.U.228.239; 3.U.228.154; 3.U.228.157;
 3.U.228.166; 3.U.228.169; 3.U.228.172; 3.U.228.175; 3.U.228.240;
 3.U.228.244; 3.U.229.228; 3.U.229.229; 3.U.229.230; 3.U.229.231;
 30 3.U.229.236; 3.U.229.237; 3.U.229.238; 3.U.229.239; 3.U.229.154;
 3.U.229.157; 3.U.229.166; 3.U.229.169; 3.U.229.172; 3.U.229.175;

- 3.U.229.240; 3.U.229.244; 3.U.230.228; 3.U.230.229; 3.U.230.230;
 3.U.230.231; 3.U.230.236; 3.U.230.237; 3.U.230.238; 3.U.230.239;
 3.U.230.154; 3.U.230.157; 3.U.230.166; 3.U.230.169; 3.U.230.172;
 3.U.230.175; 3.U.230.240; 3.U.230.244; 3.U.231.228; 3.U.231.229;
 5 3.U.231.230; 3.U.231.231; 3.U.231.236; 3.U.231.237; 3.U.231.238;
 3.U.231.239; 3.U.231.154; 3.U.231.157; 3.U.231.166; 3.U.231.169;
 3.U.231.172; 3.U.231.175; 3.U.231.240; 3.U.231.244; 3.U.236.228;
 3.U.236.229; 3.U.236.230; 3.U.236.231; 3.U.236.236; 3.U.236.237;
 3.U.236.238; 3.U.236.239; 3.U.236.154; 3.U.236.157; 3.U.236.166;
 10 3.U.236.169; 3.U.236.172; 3.U.236.175; 3.U.236.240; 3.U.236.244;
 3.U.237.228; 3.U.237.229; 3.U.237.230; 3.U.237.231; 3.U.237.236;
 3.U.237.237; 3.U.237.238; 3.U.237.239; 3.U.237.154; 3.U.237.157;
 3.U.237.166; 3.U.237.169; 3.U.237.172; 3.U.237.175; 3.U.237.240;
 3.U.237.244; 3.U.238.228; 3.U.238.229; 3.U.238.230; 3.U.238.231;
 15 3.U.238.236; 3.U.238.237; 3.U.238.238; 3.U.238.239; 3.U.238.154;
 3.U.238.157; 3.U.238.166; 3.U.238.169; 3.U.238.172; 3.U.238.175;
 3.U.238.240; 3.U.238.244; 3.U.239.228; 3.U.239.229; 3.U.239.230;
 3.U.239.231; 3.U.239.236; 3.U.239.237; 3.U.239.238; 3.U.239.239;
 3.U.239.154; 3.U.239.157; 3.U.239.166; 3.U.239.169; 3.U.239.172;
 20 3.U.239.175; 3.U.239.240; 3.U.239.244; 3.U.154.228; 3.U.154.229;
 3.U.154.230; 3.U.154.231; 3.U.154.236; 3.U.154.237; 3.U.154.238;
 3.U.154.239; 3.U.154.154; 3.U.154.157; 3.U.154.166; 3.U.154.169;
 3.U.154.172; 3.U.154.175; 3.U.154.240; 3.U.154.244; 3.U.157.228;
 3.U.157.229; 3.U.157.230; 3.U.157.231; 3.U.157.236; 3.U.157.237;
 25 3.U.157.238; 3.U.157.239; 3.U.157.154; 3.U.157.157; 3.U.157.166;
 3.U.157.169; 3.U.157.172; 3.U.157.175; 3.U.157.240; 3.U.157.244;
 3.U.166.228; 3.U.166.229; 3.U.166.230; 3.U.166.231; 3.U.166.236;
 3.U.166.237; 3.U.166.238; 3.U.166.239; 3.U.166.154; 3.U.166.157;
 3.U.166.166; 3.U.166.169; 3.U.166.172; 3.U.166.175; 3.U.166.240;
 30 3.U.166.244; 3.U.169.228; 3.U.169.229; 3.U.169.230; 3.U.169.231;
 3.U.169.236; 3.U.169.237; 3.U.169.238; 3.U.169.239; 3.U.169.154;

3.U.169.157; 3.U.169.166; 3.U.169.169; 3.U.169.172; 3.U.169.175;
3.U.169.240; 3.U.169.244; 3.U.172.228; 3.U.172.229; 3.U.172.230;
3.U.172.231; 3.U.172.236; 3.U.172.237; 3.U.172.238; 3.U.172.239;
3.U.172.154; 3.U.172.157; 3.U.172.166; 3.U.172.169; 3.U.172.172;
5 3.U.172.175; 3.U.172.240; 3.U.172.244; 3.U.175.228; 3.U.175.229;
3.U.175.230; 3.U.175.231; 3.U.175.236; 3.U.175.237; 3.U.175.238;
3.U.175.239; 3.U.175.154; 3.U.175.157; 3.U.175.166; 3.U.175.169;
3.U.175.172; 3.U.175.175; 3.U.175.240; 3.U.175.244; 3.U.240.228;
3.U.240.229; 3.U.240.230; 3.U.240.231; 3.U.240.236; 3.U.240.237;
10 3.U.240.238; 3.U.240.239; 3.U.240.154; 3.U.240.157; 3.U.240.166;
3.U.240.169; 3.U.240.172; 3.U.240.175; 3.U.240.240; 3.U.240.244;
3.U.244.228; 3.U.244.229; 3.U.244.230; 3.U.244.231; 3.U.244.236;
3.U.244.237; 3.U.244.238; 3.U.244.239; 3.U.244.154; 3.U.244.157;
3.U.244.166; 3.U.244.169; 3.U.244.172; 3.U.244.175; 3.U.244.240;
15 3.U.244.244;

Prodrugs of 3.W

3.W.228.228; 3.W.228.229; 3.W.228.230; 3.W.228.231; 3.W.228.236;
3.W.228.237; 3.W.228.238; 3.W.228.239; 3.W.228.154; 3.W.228.157;
20 3.W.228.166; 3.W.228.169; 3.W.228.172; 3.W.228.175; 3.W.228.240;
3.W.228.244; 3.W.229.228; 3.W.229.229; 3.W.229.230; 3.W.229.231;
3.W.229.236; 3.W.229.237; 3.W.229.238; 3.W.229.239; 3.W.229.154;
3.W.229.157; 3.W.229.166; 3.W.229.169; 3.W.229.172; 3.W.229.175;
3.W.229.240; 3.W.229.244; 3.W.230.228; 3.W.230.229; 3.W.230.230;
25 3.W.230.231; 3.W.230.236; 3.W.230.237; 3.W.230.238; 3.W.230.239;
3.W.230.154; 3.W.230.157; 3.W.230.166; 3.W.230.169; 3.W.230.172;
3.W.230.175; 3.W.230.240; 3.W.230.244; 3.W.231.228; 3.W.231.229;
3.W.231.230; 3.W.231.231; 3.W.231.236; 3.W.231.237; 3.W.231.238;
3.W.231.239; 3.W.231.154; 3.W.231.157; 3.W.231.166; 3.W.231.169;
30 3.W.231.172; 3.W.231.175; 3.W.231.240; 3.W.231.244; 3.W.236.228;
3.W.236.229; 3.W.236.230; 3.W.236.231; 3.W.236.236; 3.W.236.237;

3.W.236.238; 3.W.236.239; 3.W.236.154; 3.W.236.157; 3.W.236.166;
3.W.236.169; 3.W.236.172; 3.W.236.175; 3.W.236.240; 3.W.236.244;
3.W.237.228; 3.W.237.229; 3.W.237.230; 3.W.237.231; 3.W.237.236;
3.W.237.237; 3.W.237.238; 3.W.237.239; 3.W.237.154; 3.W.237.157;
5 3.W.237.166; 3.W.237.169; 3.W.237.172; 3.W.237.175; 3.W.237.240;
3.W.237.244; 3.W.238.228; 3.W.238.229; 3.W.238.230; 3.W.238.231;
3.W.238.236; 3.W.238.237; 3.W.238.238; 3.W.238.239; 3.W.238.154;
3.W.238.157; 3.W.238.166; 3.W.238.169; 3.W.238.172; 3.W.238.175;
3.W.238.240; 3.W.238.244; 3.W.239.228; 3.W.239.229; 3.W.239.230;
10 3.W.239.231; 3.W.239.236; 3.W.239.237; 3.W.239.238; 3.W.239.239;
3.W.239.154; 3.W.239.157; 3.W.239.166; 3.W.239.169; 3.W.239.172;
3.W.239.175; 3.W.239.240; 3.W.239.244; 3.W.154.228; 3.W.154.229;
3.W.154.230; 3.W.154.231; 3.W.154.236; 3.W.154.237; 3.W.154.238;
3.W.154.239; 3.W.154.154; 3.W.154.157; 3.W.154.166; 3.W.154.169;
15 3.W.154.172; 3.W.154.175; 3.W.154.240; 3.W.154.244; 3.W.157.228;
3.W.157.229; 3.W.157.230; 3.W.157.231; 3.W.157.236; 3.W.157.237;
3.W.157.238; 3.W.157.239; 3.W.157.154; 3.W.157.157; 3.W.157.166;
3.W.157.169; 3.W.157.172; 3.W.157.175; 3.W.157.240; 3.W.157.244;
3.W.166.228; 3.W.166.229; 3.W.166.230; 3.W.166.231; 3.W.166.236;
20 3.W.166.237; 3.W.166.238; 3.W.166.239; 3.W.166.154; 3.W.166.157;
3.W.166.166; 3.W.166.169; 3.W.166.172; 3.W.166.175; 3.W.166.240;
3.W.166.244; 3.W.169.228; 3.W.169.229; 3.W.169.230; 3.W.169.231;
3.W.169.236; 3.W.169.237; 3.W.169.238; 3.W.169.239; 3.W.169.154;
3.W.169.157; 3.W.169.166; 3.W.169.169; 3.W.169.172; 3.W.169.175;
25 3.W.169.240; 3.W.169.244; 3.W.172.228; 3.W.172.229; 3.W.172.230;
3.W.172.231; 3.W.172.236; 3.W.172.237; 3.W.172.238; 3.W.172.239;
3.W.172.154; 3.W.172.157; 3.W.172.166; 3.W.172.169; 3.W.172.172;
3.W.172.175; 3.W.172.240; 3.W.172.244; 3.W.175.228; 3.W.175.229;
3.W.175.230; 3.W.175.231; 3.W.175.236; 3.W.175.237; 3.W.175.238;
30 3.W.175.239; 3.W.175.154; 3.W.175.157; 3.W.175.166; 3.W.175.169;
3.W.175.172; 3.W.175.175; 3.W.175.240; 3.W.175.244; 3.W.240.228;

3.W.240.229; 3.W.240.230; 3.W.240.231; 3.W.240.236; 3.W.240.237;
 3.W.240.238; 3.W.240.239; 3.W.240.154; 3.W.240.157; 3.W.240.166;
 3.W.240.169; 3.W.240.172; 3.W.240.175; 3.W.240.240; 3.W.240.244;
 3.W.244.228; 3.W.244.229; 3.W.244.230; 3.W.244.231; 3.W.244.236;
 5 3.W.244.237; 3.W.244.238; 3.W.244.239; 3.W.244.154; 3.W.244.157;
 3.W.244.166; 3.W.244.169; 3.W.244.172; 3.W.244.175; 3.W.244.240;
 3.W.244.244;

Prodrugs of 3.Y

10 3.Y.228.228; 3.Y.228.229; 3.Y.228.230; 3.Y.228.231; 3.Y.228.236;
 3.Y.228.237; 3.Y.228.238; 3.Y.228.239; 3.Y.228.154; 3.Y.228.157; 3.Y.228.166;
 3.Y.228.169; 3.Y.228.172; 3.Y.228.175; 3.Y.228.240; 3.Y.228.244; 3.Y.229.228;
 3.Y.229.229; 3.Y.229.230; 3.Y.229.231; 3.Y.229.236; 3.Y.229.237; 3.Y.229.238;
 3.Y.229.239; 3.Y.229.154; 3.Y.229.157; 3.Y.229.166; 3.Y.229.169; 3.Y.229.172;
 15 3.Y.229.175; 3.Y.229.240; 3.Y.229.244; 3.Y.230.228; 3.Y.230.229; 3.Y.230.230;
 3.Y.230.231; 3.Y.230.236; 3.Y.230.237; 3.Y.230.238; 3.Y.230.239; 3.Y.230.154;
 3.Y.230.157; 3.Y.230.166; 3.Y.230.169; 3.Y.230.172; 3.Y.230.175; 3.Y.230.240;
 3.Y.230.244; 3.Y.231.228; 3.Y.231.229; 3.Y.231.230; 3.Y.231.231; 3.Y.231.236;
 3.Y.231.237; 3.Y.231.238; 3.Y.231.239; 3.Y.231.154; 3.Y.231.157; 3.Y.231.166;
 20 3.Y.231.169; 3.Y.231.172; 3.Y.231.175; 3.Y.231.240; 3.Y.231.244; 3.Y.236.228;
 3.Y.236.229; 3.Y.236.230; 3.Y.236.231; 3.Y.236.236; 3.Y.236.237; 3.Y.236.238;
 3.Y.236.239; 3.Y.236.154; 3.Y.236.157; 3.Y.236.166; 3.Y.236.169; 3.Y.236.172;
 3.Y.236.175; 3.Y.236.240; 3.Y.236.244; 3.Y.237.228; 3.Y.237.229; 3.Y.237.230;
 3.Y.237.231; 3.Y.237.236; 3.Y.237.237; 3.Y.237.238; 3.Y.237.239; 3.Y.237.154;
 25 3.Y.237.157; 3.Y.237.166; 3.Y.237.169; 3.Y.237.172; 3.Y.237.175; 3.Y.237.240;
 3.Y.237.244; 3.Y.238.228; 3.Y.238.229; 3.Y.238.230; 3.Y.238.231; 3.Y.238.236;
 3.Y.238.237; 3.Y.238.238; 3.Y.238.239; 3.Y.238.154; 3.Y.238.157; 3.Y.238.166;
 3.Y.238.169; 3.Y.238.172; 3.Y.238.175; 3.Y.238.240; 3.Y.238.244; 3.Y.239.228;
 3.Y.239.229; 3.Y.239.230; 3.Y.239.231; 3.Y.239.236; 3.Y.239.237; 3.Y.239.238;
 30 3.Y.239.239; 3.Y.239.154; 3.Y.239.157; 3.Y.239.166; 3.Y.239.169; 3.Y.239.172;
 3.Y.239.175; 3.Y.239.240; 3.Y.239.244; 3.Y.154.228; 3.Y.154.229; 3.Y.154.230;

3.Y.154.231; 3.Y.154.236; 3.Y.154.237; 3.Y.154.238; 3.Y.154.239; 3.Y.154.154;
3.Y.154.157; 3.Y.154.166; 3.Y.154.169; 3.Y.154.172; 3.Y.154.175; 3.Y.154.240;
3.Y.154.244; 3.Y.157.228; 3.Y.157.229; 3.Y.157.230; 3.Y.157.231; 3.Y.157.236;
3.Y.157.237; 3.Y.157.238; 3.Y.157.239; 3.Y.157.154; 3.Y.157.157; 3.Y.157.166;
5 3.Y.157.169; 3.Y.157.172; 3.Y.157.175; 3.Y.157.240; 3.Y.157.244; 3.Y.166.228;
3.Y.166.229; 3.Y.166.230; 3.Y.166.231; 3.Y.166.236; 3.Y.166.237; 3.Y.166.238;
3.Y.166.239; 3.Y.166.154; 3.Y.166.157; 3.Y.166.166; 3.Y.166.169; 3.Y.166.172;
3.Y.166.175; 3.Y.166.240; 3.Y.166.244; 3.Y.169.228; 3.Y.169.229; 3.Y.169.230;
3.Y.169.231; 3.Y.169.236; 3.Y.169.237; 3.Y.169.238; 3.Y.169.239; 3.Y.169.154;
10 3.Y.169.157; 3.Y.169.166; 3.Y.169.169; 3.Y.169.172; 3.Y.169.175; 3.Y.169.240;
3.Y.169.244; 3.Y.172.228; 3.Y.172.229; 3.Y.172.230; 3.Y.172.231; 3.Y.172.236;
3.Y.172.237; 3.Y.172.238; 3.Y.172.239; 3.Y.172.154; 3.Y.172.157; 3.Y.172.166;
3.Y.172.169; 3.Y.172.172; 3.Y.172.175; 3.Y.172.240; 3.Y.172.244; 3.Y.175.228;
3.Y.175.229; 3.Y.175.230; 3.Y.175.231; 3.Y.175.236; 3.Y.175.237; 3.Y.175.238;
15 3.Y.175.239; 3.Y.175.154; 3.Y.175.157; 3.Y.175.166; 3.Y.175.169; 3.Y.175.172;
3.Y.175.175; 3.Y.175.240; 3.Y.175.244; 3.Y.240.228; 3.Y.240.229; 3.Y.240.230;
3.Y.240.231; 3.Y.240.236; 3.Y.240.237; 3.Y.240.238; 3.Y.240.239; 3.Y.240.154;
3.Y.240.157; 3.Y.240.166; 3.Y.240.169; 3.Y.240.172; 3.Y.240.175; 3.Y.240.240;
3.Y.240.244; 3.Y.244.228; 3.Y.244.229; 3.Y.244.230; 3.Y.244.231; 3.Y.244.236;
20 3.Y.244.237; 3.Y.244.238; 3.Y.244.239; 3.Y.244.154; 3.Y.244.157; 3.Y.244.166;
3.Y.244.169; 3.Y.244.172; 3.Y.244.175; 3.Y.244.240; 3.Y.244.244;

Prodrugs of 4.B

4.B.228.228; 4.B.228.229; 4.B.228.230; 4.B.228.231; 4.B.228.236;
25 4.B.228.237; 4.B.228.238; 4.B.228.239; 4.B.228.154; 4.B.228.157; 4.B.228.166;
4.B.228.169; 4.B.228.172; 4.B.228.175; 4.B.228.240; 4.B.228.244; 4.B.229.228;
4.B.229.229; 4.B.229.230; 4.B.229.231; 4.B.229.236; 4.B.229.237; 4.B.229.238;
4.B.229.239; 4.B.229.154; 4.B.229.157; 4.B.229.166; 4.B.229.169; 4.B.229.172;
4.B.229.175; 4.B.229.240; 4.B.229.244; 4.B.230.228; 4.B.230.229; 4.B.230.230;
30 4.B.230.231; 4.B.230.236; 4.B.230.237; 4.B.230.238; 4.B.230.239; 4.B.230.154;
4.B.230.157; 4.B.230.166; 4.B.230.169; 4.B.230.172; 4.B.230.175; 4.B.230.240;

4.B.230.244; 4.B.231.228; 4.B.231.229; 4.B.231.230; 4.B.231.231; 4.B.231.236;
4.B.231.237; 4.B.231.238; 4.B.231.239; 4.B.231.154; 4.B.231.157; 4.B.231.166;
4.B.231.169; 4.B.231.172; 4.B.231.175; 4.B.231.240; 4.B.231.244; 4.B.236.228;
4.B.236.229; 4.B.236.230; 4.B.236.231; 4.B.236.236; 4.B.236.237; 4.B.236.238;
5 4.B.236.239; 4.B.236.154; 4.B.236.157; 4.B.236.166; 4.B.236.169; 4.B.236.172;
4.B.236.175; 4.B.236.240; 4.B.236.244; 4.B.237.228; 4.B.237.229; 4.B.237.230;
4.B.237.231; 4.B.237.236; 4.B.237.237; 4.B.237.238; 4.B.237.239; 4.B.237.154;
4.B.237.157; 4.B.237.166; 4.B.237.169; 4.B.237.172; 4.B.237.175; 4.B.237.240;
4.B.237.244; 4.B.238.228; 4.B.238.229; 4.B.238.230; 4.B.238.231; 4.B.238.236;
10 4.B.238.237; 4.B.238.238; 4.B.238.239; 4.B.238.154; 4.B.238.157; 4.B.238.166;
4.B.238.169; 4.B.238.172; 4.B.238.175; 4.B.238.240; 4.B.238.244; 4.B.239.228;
4.B.239.229; 4.B.239.230; 4.B.239.231; 4.B.239.236; 4.B.239.237; 4.B.239.238;
4.B.239.239; 4.B.239.154; 4.B.239.157; 4.B.239.166; 4.B.239.169; 4.B.239.172;
4.B.239.175; 4.B.239.240; 4.B.239.244; 4.B.154.228; 4.B.154.229; 4.B.154.230;
15 4.B.154.231; 4.B.154.236; 4.B.154.237; 4.B.154.238; 4.B.154.239; 4.B.154.154;
4.B.154.157; 4.B.154.166; 4.B.154.169; 4.B.154.172; 4.B.154.175; 4.B.154.240;
4.B.154.244; 4.B.157.228; 4.B.157.229; 4.B.157.230; 4.B.157.231; 4.B.157.236;
4.B.157.237; 4.B.157.238; 4.B.157.239; 4.B.157.154; 4.B.157.157; 4.B.157.166;
4.B.157.169; 4.B.157.172; 4.B.157.175; 4.B.157.240; 4.B.157.244; 4.B.166.228;
20 4.B.166.229; 4.B.166.230; 4.B.166.231; 4.B.166.236; 4.B.166.237; 4.B.166.238;
4.B.166.239; 4.B.166.154; 4.B.166.157; 4.B.166.166; 4.B.166.169; 4.B.166.172;
4.B.166.175; 4.B.166.240; 4.B.166.244; 4.B.169.228; 4.B.169.229; 4.B.169.230;
4.B.169.231; 4.B.169.236; 4.B.169.237; 4.B.169.238; 4.B.169.239; 4.B.169.154;
4.B.169.157; 4.B.169.166; 4.B.169.169; 4.B.169.172; 4.B.169.175; 4.B.169.240;
25 4.B.169.244; 4.B.172.228; 4.B.172.229; 4.B.172.230; 4.B.172.231; 4.B.172.236;
4.B.172.237; 4.B.172.238; 4.B.172.239; 4.B.172.154; 4.B.172.157; 4.B.172.166;
4.B.172.169; 4.B.172.172; 4.B.172.175; 4.B.172.240; 4.B.172.244; 4.B.175.228;
4.B.175.229; 4.B.175.230; 4.B.175.231; 4.B.175.236; 4.B.175.237; 4.B.175.238;
4.B.175.239; 4.B.175.154; 4.B.175.157; 4.B.175.166; 4.B.175.169; 4.B.175.172;
30 4.B.175.175; 4.B.175.240; 4.B.175.244; 4.B.240.228; 4.B.240.229; 4.B.240.230;
4.B.240.231; 4.B.240.236; 4.B.240.237; 4.B.240.238; 4.B.240.239; 4.B.240.154;

4.B.240.157; 4.B.240.166; 4.B.240.169; 4.B.240.172; 4.B.240.175; 4.B.240.240;
4.B.240.244; 4.B.244.228; 4.B.244.229; 4.B.244.230; 4.B.244.231; 4.B.244.236;
4.B.244.237; 4.B.244.238; 4.B.244.239; 4.B.244.154; 4.B.244.157; 4.B.244.166;
4.B.244.169; 4.B.244.172; 4.B.244.175; 4.B.244.240; 4.B.244.244;

5

Prodrugs of 4.D

4.D.228.228; 4.D.228.229; 4.D.228.230; 4.D.228.231; 4.D.228.236;
4.D.228.237; 4.D.228.238; 4.D.228.239; 4.D.228.154; 4.D.228.157;
4.D.228.166; 4.D.228.169; 4.D.228.172; 4.D.228.175; 4.D.228.240;
10 4.D.228.244; 4.D.229.228; 4.D.229.229; 4.D.229.230; 4.D.229.231;
4.D.229.236; 4.D.229.237; 4.D.229.238; 4.D.229.239; 4.D.229.154;
4.D.229.157; 4.D.229.166; 4.D.229.169; 4.D.229.172; 4.D.229.175;
4.D.229.240; 4.D.229.244; 4.D.230.228; 4.D.230.229; 4.D.230.230;
4.D.230.231; 4.D.230.236; 4.D.230.237; 4.D.230.238; 4.D.230.239;
15 4.D.230.154; 4.D.230.157; 4.D.230.166; 4.D.230.169; 4.D.230.172;
4.D.230.175; 4.D.230.240; 4.D.230.244; 4.D.231.228; 4.D.231.229;
4.D.231.230; 4.D.231.231; 4.D.231.236; 4.D.231.237; 4.D.231.238;
4.D.231.239; 4.D.231.154; 4.D.231.157; 4.D.231.166; 4.D.231.169;
4.D.231.172; 4.D.231.175; 4.D.231.240; 4.D.231.244; 4.D.236.228;
20 4.D.236.229; 4.D.236.230; 4.D.236.231; 4.D.236.236; 4.D.236.237;
4.D.236.238; 4.D.236.239; 4.D.236.154; 4.D.236.157; 4.D.236.166;
4.D.236.169; 4.D.236.172; 4.D.236.175; 4.D.236.240; 4.D.236.244;
4.D.237.228; 4.D.237.229; 4.D.237.230; 4.D.237.231; 4.D.237.236;
4.D.237.237; 4.D.237.238; 4.D.237.239; 4.D.237.154; 4.D.237.157;
25 4.D.237.166; 4.D.237.169; 4.D.237.172; 4.D.237.175; 4.D.237.240;
4.D.237.244; 4.D.238.228; 4.D.238.229; 4.D.238.230; 4.D.238.231;
4.D.238.236; 4.D.238.237; 4.D.238.238; 4.D.238.239; 4.D.238.154;
4.D.238.157; 4.D.238.166; 4.D.238.169; 4.D.238.172; 4.D.238.175;
4.D.238.240; 4.D.238.244; 4.D.239.228; 4.D.239.229; 4.D.239.230;
30 4.D.239.231; 4.D.239.236; 4.D.239.237; 4.D.239.238; 4.D.239.239;
4.D.239.154; 4.D.239.157; 4.D.239.166; 4.D.239.169; 4.D.239.172;

- 4.D.239.175; 4.D.239.240; 4.D.239.244; 4.D.154.228; 4.D.154.229;
4.D.154.230; 4.D.154.231; 4.D.154.236; 4.D.154.237; 4.D.154.238;
4.D.154.239; 4.D.154.154; 4.D.154.157; 4.D.154.166; 4.D.154.169;
4.D.154.172; 4.D.154.175; 4.D.154.240; 4.D.154.244; 4.D.157.228;
5 4.D.157.229; 4.D.157.230; 4.D.157.231; 4.D.157.236; 4.D.157.237;
4.D.157.238; 4.D.157.239; 4.D.157.154; 4.D.157.157; 4.D.157.166;
4.D.157.169; 4.D.157.172; 4.D.157.175; 4.D.157.240; 4.D.157.244;
4.D.166.228; 4.D.166.229; 4.D.166.230; 4.D.166.231; 4.D.166.236;
4.D.166.237; 4.D.166.238; 4.D.166.239; 4.D.166.154; 4.D.166.157;
10 4.D.166.166; 4.D.166.169; 4.D.166.172; 4.D.166.175; 4.D.166.240;
4.D.166.244; 4.D.169.228; 4.D.169.229; 4.D.169.230; 4.D.169.231;
4.D.169.236; 4.D.169.237; 4.D.169.238; 4.D.169.239; 4.D.169.154;
4.D.169.157; 4.D.169.166; 4.D.169.169; 4.D.169.172; 4.D.169.175;
4.D.169.240; 4.D.169.244; 4.D.172.228; 4.D.172.229; 4.D.172.230;
15 4.D.172.231; 4.D.172.236; 4.D.172.237; 4.D.172.238; 4.D.172.239;
4.D.172.154; 4.D.172.157; 4.D.172.166; 4.D.172.169; 4.D.172.172;
4.D.172.175; 4.D.172.240; 4.D.172.244; 4.D.175.228; 4.D.175.229;
4.D.175.230; 4.D.175.231; 4.D.175.236; 4.D.175.237; 4.D.175.238;
4.D.175.239; 4.D.175.154; 4.D.175.157; 4.D.175.166; 4.D.175.169;
20 4.D.175.172; 4.D.175.175; 4.D.175.240; 4.D.175.244; 4.D.240.228;
4.D.240.229; 4.D.240.230; 4.D.240.231; 4.D.240.236; 4.D.240.237;
4.D.240.238; 4.D.240.239; 4.D.240.154; 4.D.240.157; 4.D.240.166;
4.D.240.169; 4.D.240.172; 4.D.240.175; 4.D.240.240; 4.D.240.244;
4.D.244.228; 4.D.244.229; 4.D.244.230; 4.D.244.231; 4.D.244.236;
25 4.D.244.237; 4.D.244.238; 4.D.244.239; 4.D.244.154; 4.D.244.157;
4.D.244.166; 4.D.244.169; 4.D.244.172; 4.D.244.175; 4.D.244.240;
4.D.244.244;

Prodrugs of 4.E

- 30 4.E.228.228; 4.E.228.229; 4.E.228.230; 4.E.228.231; 4.E.228.236;
4.E.228.237; 4.E.228.238; 4.E.228.239; 4.E.228.154; 4.E.228.157; 4.E.228.166;

- 4.E.228.169; 4.E.228.172; 4.E.228.175; 4.E.228.240; 4.E.228.244; 4.E.229.228;
4.E.229.229; 4.E.229.230; 4.E.229.231; 4.E.229.236; 4.E.229.237; 4.E.229.238;
4.E.229.239; 4.E.229.154; 4.E.229.157; 4.E.229.166; 4.E.229.169; 4.E.229.172;
4.E.229.175; 4.E.229.240; 4.E.229.244; 4.E.230.228; 4.E.230.229; 4.E.230.230;
5 4.E.230.231; 4.E.230.236; 4.E.230.237; 4.E.230.238; 4.E.230.239; 4.E.230.154;
4.E.230.157; 4.E.230.166; 4.E.230.169; 4.E.230.172; 4.E.230.175; 4.E.230.240;
4.E.230.244; 4.E.231.228; 4.E.231.229; 4.E.231.230; 4.E.231.231; 4.E.231.236;
4.E.231.237; 4.E.231.238; 4.E.231.239; 4.E.231.154; 4.E.231.157; 4.E.231.166;
4.E.231.169; 4.E.231.172; 4.E.231.175; 4.E.231.240; 4.E.231.244; 4.E.236.228;
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4.E.236.239; 4.E.236.154; 4.E.236.157; 4.E.236.166; 4.E.236.169; 4.E.236.172;
4.E.236.175; 4.E.236.240; 4.E.236.244; 4.E.237.228; 4.E.237.229; 4.E.237.230;
4.E.237.231; 4.E.237.236; 4.E.237.237; 4.E.237.238; 4.E.237.239; 4.E.237.154;
4.E.237.157; 4.E.237.166; 4.E.237.169; 4.E.237.172; 4.E.237.175; 4.E.237.240;
15 4.E.237.244; 4.E.238.228; 4.E.238.229; 4.E.238.230; 4.E.238.231; 4.E.238.236;
4.E.238.237; 4.E.238.238; 4.E.238.239; 4.E.238.154; 4.E.238.157; 4.E.238.166;
4.E.238.169; 4.E.238.172; 4.E.238.175; 4.E.238.240; 4.E.238.244; 4.E.239.228;
4.E.239.229; 4.E.239.230; 4.E.239.231; 4.E.239.236; 4.E.239.237; 4.E.239.238;
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4.E.154.157; 4.E.154.166; 4.E.154.169; 4.E.154.172; 4.E.154.175; 4.E.154.240;
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4.E.169.244; 4.E.172.228; 4.E.172.229; 4.E.172.230; 4.E.172.231; 4.E.172.236;

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4.E.175.229; 4.E.175.230; 4.E.175.231; 4.E.175.236; 4.E.175.237; 4.E.175.238;
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4.E.244.237; 4.E.244.238; 4.E.244.239; 4.E.244.154; 4.E.244.157; 4.E.244.166;
10 4.E.244.169; 4.E.244.172; 4.E.244.175; 4.E.244.240; 4.E.244.244;

Prodrugs of 4.G

4.G.228.228; 4.G.228.229; 4.G.228.230; 4.G.228.231; 4.G.228.236;
4.G.228.237; 4.G.228.238; 4.G.228.239; 4.G.228.154; 4.G.228.157;
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4.G.240.169; 4.G.240.172; 4.G.240.175; 4.G.240.240; 4.G.240.244;
30 4.G.244.228; 4.G.244.229; 4.G.244.230; 4.G.244.231; 4.G.244.236;
4.G.244.237; 4.G.244.238; 4.G.244.239; 4.G.244.154; 4.G.244.157;